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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07K

A2

(11) International Publication Number: WO 00/09537

(43) International Publication Date: 24 February 2000 (24.02.00)

(21) International Application Number: PCT/US99/17867

(22) International Filing Date: 6 August 1999 (06.08.99)

(30) Priority Data:

60/096,795	14 August 1998 (14.08.98)	US
60/129,806	16 April 1999 (16.04.99)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application

US	Not furnished (CIP)
Filed on	Not furnished

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOUNDS HAVING GROWTH HORMONE RELEASING ACTIVITY

(57) Abstract

Compounds that promote growth hormone releasing activity are disclosed. These compounds have the formula: A_1–A_2–X; A_1–X', or A_1–Y. These compounds can be present in a pharmaceutical composition. The compounds can be used with a second compound that acts as an agonist at the growth hormone releasing hormone receptor or which inhibits the effects of somatostatin. These compounds can be used for a variety of uses such as treating hypothalamic pituitary dwarfism, osteoporosis, burns, or promoting wound healing.

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COMPOUNDS HAVING GROWTH HORMONE RELEASING ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel compounds that promote the release of growth hormones when introduced to animals, preferably humans, and methods of use thereof.

BACKGROUND OF THE INVENTION

The elevation of growth hormone (GH) levels in animals, e.g., mammals including humans, upon administration of GH-releasing compounds can lead to enhanced body weight and to enhanced milk production if sufficiently elevated GH levels occur upon administration. Further, it is known that the elevation of growth hormone levels in mammals and humans can be accomplished by application of known growth hormone releasing agents, such as the naturally occurring growth hormone releasing hormones.

The elevation of growth hormone levels in mammals can also be accomplished by application of growth hormone releasing peptides (GHRPs), some of which have been previously described, for example, in U.S. 4,223,019; U.S. 4,223,020; U.S. 4,223,021; U.S. 4,224,316; U.S. 4,226,857; U.S. 4,228,155; U.S. 4,228,156; U.S. 4,228,157; U.S. 4,228,158; U.S. 4,410,512; U.S. 4,410,513.

Antibodies to the endogenous growth hormone release inhibitor, somatostatin (SRIF) have also been used to cause elevated GH levels. In this latter example, growth hormone levels are elevated by removing the endogenous GH-release inhibitor (SRIF) before it reaches the pituitary, where it inhibits the release of GH.

These methods for promoting the elevation of growth hormone levels frequently involve materials which are expensive to synthesize and/or difficult to isolate in sufficient purity for administration to a target animal. Low molecular weight, relatively simple and inexpensive compounds that

have the ability to promote the release of growth hormone would be desirable in that they could be readily and inexpensively prepared, easily modified chemically and/or physically, as well as easily purified and formulated, and designed to have improved transport properties.

GH and/or GHRPs have been administered to stimulate growth hormone production and/or release, for example, to stimulate growth, enhance milk production, enhance body weight, increase rate of protein synthesis, reduce rate of carbohydrate utilization, increase mobilization of pre-fatty acids. Although the use of many of these compounds such as a series of short peptides (e.g., U.S. Patent Nos. 5,663,146 and 5,486,505) have been important steps in the design and delivery of compounds having GH and/or GHRP properties, improvements can still be made. For example, improvements can be made in the areas of oral bioavailability, serum retention time, etc.

Non-peptidal or hybrid-peptidal secretagogues have also been described. See U.S. Patent Nos. 5,494,919; 5,492,920; 5,492,916; 5,622,973; WO95/13069, WO96/15148; WO96/35713; WO97/22367; WO97/00894; WO97/07117; and WO97/11697. Despite the general descriptions of such compounds, it is not possible to make broad generalizations about which particular compounds are favorable. Although some secretagogues, which can promote the release and elevation of growth hormone levels in the blood, have been described, corresponding data on the biological activity has often been lacking. Moreover, even in terms of tripeptides with or without C-terminal modifications, the data suggests that it has heretofore been impossible to make the broad sweeping generalization made in those publications about what would or would not be a favorable amino acid combination at the three positions of a tripeptide holding the C-terminal constant or holding the peptidal portion constant while making changes, or changing the chemical moieties added. Changes in any of the constituents can have great effects on activity. It is submitted that these references do not lead to general teachings of biological efficacy.

In order to maximize the ability to select and tailor a compound, it would be desirable to have a class of compounds that generally provide good growth hormone releasing effects and have at least one other desirable

biological activity such as better bioavailability, absorption, metabolism, pharmacokinetics, excretions, etc. It would also be desirable to have compounds which can promote the release and elevation of growth hormone levels in the blood of animals, particularly in humans, to be able to use such compounds to promote the release and/or elevation of growth hormone levels in the blood of animals and humans, and to provide methods for promoting the release and/or elevation of growth hormone levels in the blood of animals using such compounds.

The aforementioned discussion illustrates that a broad chemical diversity of synthetic GHRPs ranging from peptides to partial peptides to non-peptides. Overall, the peptides and partial peptides have been the most effective in promoting elevated growth hormone levels. For example, partial peptides consisting of natural and unnatural amino acids of different chain lengths and C-terminal amide groups or a substituted amide with various organic chemical groups. Results published as early as 1982 stated that certain GHRPs with only 3-7 amino acids released GH and that having a D-amino acid at certain positions was useful. From 1982 to the present, GHRPs with more potent GH releasing activity have been developed. This research taught that certain amino acid positions could have certain substitutions but not others, and that one amino acid residue could affect what other substitutions could be made.

Until compounds having the optimum physical-chemical properties and physiological-biological actions and effects are discovered for various diagnostic and therapeutic uses in humans, it is important to discover a general chemical approach that will result in new types of GHRPs. Such a broader GHRP chemical base will make it possible to better implement and refine the GHRP approach.

Properties of GHRPs that are important include that they are effective when administered orally. In addition, the compound should augment the normal pulsatile physiological secretion of GH. In some subjects with decreased GH secretion, GH can be replaced in a physiological way. Physiological replacement of a hormonal deficiency improves health while minimizing the potential adverse action of the hormone. This is especially important in treating older men and women, as they may be particularly

susceptible to the adverse effects of over-treatment with GH. Already, chronic administration of GHRPs to animals and humans has produced anabolic effects. Body weight gain has been increased in rats, milk production has been increased in cows. Additionally, when a compound such as DAla-DβNal-Ala-Trp-DPhe-Lys-NH_2 (GHRP-2) was administered to short-statured children with various degrees of GH deficiency 2-3 times per day over a 2 year period, the rate of height velocity has been accelerated in those children.

In principle, the anabolic biological effects of GHRPs emphasize the potential clinical value of the GHRP approach. The finding that GHRP-2 is less effective on height velocity than usually obtained with chronic recombinant human growth hormone (rhGH) administration, underscores the desirability for improving the GHRP approach. This includes further optimization and extension of the range of the GHRP chemistry in order to produce more effective biological actions.

In looking at these compounds, one looks at a varied series of biological effects such as the duration of action of GHRP. Other parameters that may substantially be affected by the chemistry of the GHRP include desensitization of the GHRP GH response, actions on the hypothalamus, effects on SRIF release and action, effects on ACTH and PRL release as well as possible effects on putative subclasses of GHRP receptors. All of these actions are directly and/or indirectly dependent on the GHRP chemistry, pattern and efficiency of oral absorption as well as the metabolism and secretion of the particular GHRP.

SUMMARY OF THE INVENTION

We have now discovered a new group of compounds (sometimes referred to as secretagogues) that provide desirable *in vitro* and *in vivo* growth hormone releasing activity and have at least one other desirable biological activity such as increased retention time. These compounds have the following formulas:

Formula I: A_1-A_2-X

wherein A_1 is Aib (aminoisobutyric acid), inip (isonipecotyl) or ABU (aminobutyric acid). The Aib residue can be substituted or unsubstituted.

Preferred substituents include C_1-C_6 alkyl and halogens. Aib is preferably unsubstituted. Aib is preferably αAib. ABU is preferably γABU or αγABU, more preferably α,γABU;

A_2 is any natural L-amino acid or Pal, or their respective D-isomers, DαNal (α-naphthyl-D-alanine) or DβNal (β-naphthyl-D-alanine), preferably A_2 is DTrp, DαNal (α-naphthyl-D-alanine) or DβNal (β-naphthyl-D-alanine), more preferably A_2 is DTrp or DαNal;

X is (1) R_1-R_2-Z, wherein R_1 and R_2 are any natural L-amino acid, Pal, αNal, βNal, DpCl, CHx, where CH_x is cyclohexyl, CHxAla, or any of their respective D-isomers, preferably R_1 is DPro, DTrp, DβNal or DPhe, more preferably R_1 is DPro or DTrp; and R_2 is preferably Gly, Phe, Pro, DPro, DPhe, DPal, DLeu, DHis, DVal, DGln, DArg, DAla, DSer, DThr, DIle, Arg, Orn Lys, Ala, Pal, Thr, Val, PheCHx, CHxAla or CHx, where x is preferably 1-8, more preferably 1 to 5; and Z is $CONH_2$ or COOH;

(2) DpR_3Phe-R_4-Z, wherein R_3 is a halogen, preferably Cl, and R_4 is any natural L-amino acid or Pal, or their respective D-isomers, preferably R_4 is Phe or Arg, and Z is $CONH_2$ or COOH;

(3) $NH(CH_2)_nNH$, where n is 1 to 8, such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide;

(4) R_5-R_6, wherein R_5 is any natural L-amino acid, Pal, αNal, βNal, DpCl, CHx where x is 1 to 10, or any of their respective D-isomers, preferably R_5 is DPro or DTrp, and R_6 is

(a) diisobutylamide

(b) dipropylamide

(c) butylamide

(d) pentylamide

(e) dipentylamide

(f) C(=0) (substituted heteroalicyclic or heteroaromatic) such as -piperidine-3-methyl-

benzylether

-N-diethylnipectamide

-N-piperazine methylsulfonamide
-diethylamide
-m-methylpiperidine
-3,3-diphenylpropylamide
-4-piperidino piperidinamide
-4-phenyl-piperidinamide
-N-methylpiperazine
-2-morpholinoethylamine
-spiroindole methylsulfonamide
-pyrrolidine amide
-indoleamide
-3-piperidine methanolamide
-tropin amide
-2-aminoethylamide
-3-aminopropylamide
-4-aminobutylamide
-5-aminopentylamide
-6-aminohexylamide;

(5) DTrp Phe ArgR_7, wherein R_7 is $NH(CH_2)_nNH$, where n is 1 to 8, such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide; or

(6) R_8-R_9-R_{10}-Z, wherein R_8 is DTrp, DPro, DαNal or DβNal, preferably R_8 is DTrp or DPro, R_9 is any natural L-amino acid or Pal, or their respective D-isomers, preferably R_9 is Phe, DVal, DPro, DIle, Ile, more preferably R_9 is Phe, DVal or DPro; R_{10} is any natural L-amino acid or Pal, or their respective D-isomers, preferably R_{10} is Lys or Arg, and Z is $CONH_2$ or COOH, preferably Z is $CONH_2$.

Formula II: A_1-X'

wherein A_1 is Aib, inip, ABU, IMC (imidazole carboxylic acid), Ava, 4-IMA (Nα-imidazole acetic acid), βAla, Ileu, Trp, His, DpCl, CHx, or any of their respective D-isomers. The Aib residue can be substituted or unsubstituted. Preferred substituents include N- and N-,N- C_1-C_6 alkyl, halogens, N- and N-,N-2 hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and 3-hydroxyisobutyl.

Aib is preferably unsubstituted. Aib is preferably αAib. ABU is preferably γABU or αγABU, more preferably α,γABU; and

X' is (1) $R_{1'}$-$R_{2'}$-Z, wherein $R_{1'}$ is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal, preferably $R_{1'}$ is DTrp, DαNal or DβNal, more preferably $R_{1'}$ is DTrp or DαNal, and $R_{2'}$ is any natural L-amino acid, Pal, αNal, βNal, DpCl, Aib, preferably αAib, CHx where x is 1 to 10, or CHxAla, or any of their respective D-isomers, and Z is $CONH_2$ or COOH, preferably Z is $CONH_2$; or

(2) $R_{3'}$-$R_{4'}$, wherein $R_{3'}$ is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal, preferably R_3 is DPro, DTrp, DαNal or DβNal, more preferably $R_{3'}$ is DPro, DTrp or DαNal, and $R_{4'}$ is $NH(CH_2)_nNH$, where n is 1 to 8, such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide.

The organic and inorganic addition salts thereof are also included.

In an alternative embodiment the compound has the formula

Formula III: $A_{1''}$-Y,

wherein $A_{1'}$ is Aib, inip, ABU, βAla, His, Sar or any of their respective D-isomers. The Aib residue can be substituted or unsubstituted. Preferred substituents include N- and N-, N-C_1-C_6 alkyl, halogens, N- and N-, N-2 hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and 3-hydroxyisobutyl. Aib is preferably unsubstituted. $A_{1'}$ is preferably Aib, inip or ABU. More preferably Aib is αAib. Abu is preferably γAbu or α,γAbu, more preferably α,γAbu.

Y is $A_{2''}$-A_3-A_4-A_5-A_6-Z',

$A_{2''}$-A_3-A_4-A_5-Z' or $A_{2''}$-A_3-A_4-Z'

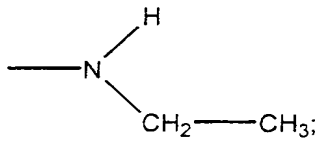
wherein $A_{2'}$ is A_5-$A_{2''}$ or $A_{2''}$,

wherein A_5 is a spacer amino acid such as His,

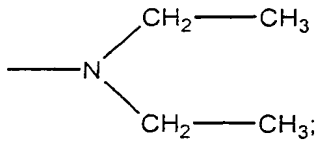
$A_{2''}$ is as defined above for A_2. $A_{2''}$ is preferably DTrp, DαNal or DβNal. $A_{2''}$ is more preferably DTrp.

A_3, A_4 and A_5 are any natural L-amino acid, Pal, αNal, βNal, Nle, Arg-DPro, DPCl, D or L (CHX), cyclohexylalanine (CHXAla), or any of their respective D-isomers, preferably A_3 is DPro, DTrp, DβNal or DPhe, more preferably A_3 is DPro or DTrp; and A_4 is preferably Gly, Phe, Pro, Ile, DPro, DPhe, DPal, DLeu, DHis, DVal, DGln, DIle, DNle, DArg, DAla, DSer, DThr, DIle, Arg, Orn Lys, Ala, Pal, Thr, Val, PheCHX, CHXAla or CHX. A_4 is preferably DSer, DAug, DPro, DTrp, DVal, DIle, DThr, DNVal, DNle, Ile, Pro, Phe and still more preferably, A_4 is DPro. A_5 is preferably Ile, Arg, Pal, DArg, DSer, Lys and Arg-DPro. More preferably A_5 is Arg, DArg, and Lys.

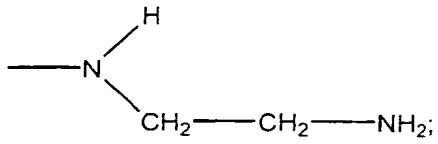
Z' is NH_2, OH or alkylamino or aminoalkylamino, preferably the alkylamino is NH (C_1-C_{10} alkyl) e.g. $NH(CH_2)_nCH_3$, where n is 1 to 10 such as



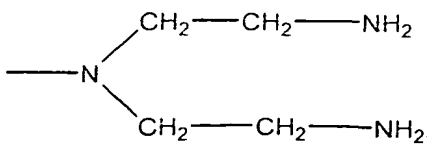
N di-(C_1-C_{10} alkyl) e.g., N di-$(CH_2)_n$ CH_3 such as



preferably the aminoalkylamino is a NH (C_1-C_{10} alkylamino, e.g. $NH(CH_2)_nNH_2$ such as



N (di C_1-C_{10} alkylamino), e.g., N [di-$(CH_2)_nNH_2$] such as



These compounds can be administered to an animal to promote release of serum growth hormone levels. Thus, these secretagogues can be used in a range of methods for example, to increase milk production, enhance body growth, treat hypothalmic pituitary dwarfism, osteoporosis, burns and renal failure, and to promote wound healing. They can also be used diagnostically. For example, to discover a loss of growth hormone receptor functioning.

DETAILED DESCRIPTION OF THE INVENTION

The compounds described herein are typically easy to synthesize, have efficacy at promoting an increase in serum growth hormone levels, and are desirable for large scale production and utilization. In addition, these compounds may be advantageous in having physiochemical properties which are desirable for the efficient delivery of such polypeptide compounds to a wide variety of animal species because of an improvement in at least one of bioavailability, absorption, metabolism, pharmacokinetics and excretion. The preferred methods of delivery are oral, nasal and continuous delivery utilizing special chemical/mechanical methods of delivery. Pulsed therapy is one preferred method of administration. These compounds have either of the following two formulas:

Formula I: A_1-A_2-X

wherein A_1 is Aib (aminoisobutyric acid), inip (isonipecotyl) or ABU (aminobutyric acid). The Aib residue can be substituted or unsubstituted. Preferred substituents include C_1-C_6 alkyl and halogens. Aib is preferably unsubstituted. Aib is preferably αAib. ABU is preferably γABU or αγABU, more preferably α,γABU;

A_2 is any natural L-amino acid or Pal, or their respective D-isomers, DαNal (α-naphthyl-D-alanine) or DβNal (β-naphthyl-D-alanine), preferably A_2 is DTrp, DαNal (α-naphthyl-D-alanine) or DβNal (β-naphthyl-D-alanine), more preferably A_2 is DTrp or DαNal;

X is (1) R_1-R_2-Z, wherein R_1 and R_2 are any natural L-amino acid, Pal, αNal, βNal, DpCl, CHx, CHxAla, or any of their respective D-isomers, preferably R_1 is DPro, DTrp, DβNal or DPhe, more preferably R_1 is

DPro or DTrp; and R_2 is preferably Gly, Phe, Pro, DPro, DPhe, DPal, DLeu, DHis, DVal, DGln, DArg, DAla, DSer, DThr, DIle, Arg, Orn Lys, Ala, Pal, Thr, Val, PheCHx, CHxAla or CHx, where x is preferably 1-8, more preferably 1 to 5; and Z is $CONH_2$ or COOH;

(2) $DpR_3Phe\text{-}R_4\text{-}Z$, wherein R_3 is a halogen, preferably Cl, and R_4 is any natural L-amino acid or Pal, or their respective D-isomers, preferably R_4 is Phe or Arg, and Z is $CONH_2$ or COOH;

(3) $NH(CH_2)_nNH$, where n is 1 to 8, such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide;

(4) $R_5\text{-}R_6$, wherein R_5 is any natural L-amino acid, Pal, αNal, βNal, DpCl, CHx where x is 1 to 10, or any of their respective D-isomers, preferably R_5 is DPro or DTrp, and R_6 is

(a) diisobutylamide
(b) dipropylamide
(c) butylamide
(d) pentylamide
(e) dipentylamide
(f) C(=0)(substituted heteroalicyclic or heteroaromatic)

such as -piperidine-3-methyl-
benzylether
-N-diethylnipectamide
-N-piperazine methylsulfonamide
-diethylamide
-m-methylpiperidine
-3,3-diphenylpropylamide
-4-piperidino piperidinamide
-4-phenyl-piperidinamide
-N-methylpiperazine
-2-morpholinoethylamine
-spiroindole methylsulfonamide
-pyrrolidine amide
-indoleamide
-3-piperidine methanolamide

-tropin amide
-2-aminoethylamide
-3-aminopropylamide
-4-aminobutylamide
-5-aminopentylamide
-6-aminohexylamide;

(5) DTrp Phe Arg R_7, wherein R_7 is $NH(CH_2)_nNH$, where n is 1 to 8, such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide; or

(6) R_8-R_9-R_{10}-Z, wherein R_8 is DTrp, DPro, DαNal or DβNal, preferably R_8 is DTrp or DPro, R_9 is any natural L-amino acid or Pal, or their respective D-isomers, preferably R_9 is Phe, DVal, DPro, DIle, Ile, more preferably R_9 is Phe, DVal or DPro; R_{10} is any natural L-amino acid or Pal, or their respective D-isomers, preferably R_{10} is Lys or Arg, and Z is $CONH_2$ or COOH, preferably Z is $CONH_2$.

Formula II: $A_{1'}$-X'

wherein $A_{1'}$ is Aib, inip, ABU, IMC (imidazole carboxylic acid), Ava, 4-IMA (Nα-imidazole acetic acid), βAla, Ileu, Trp, His, DpCl, CHx, or any of their respective D-isomers. The Aib residue can be substituted or unsubstituted. Preferred substituents include N- and N-,N- C_1-C_6 alkyl, halogens, N- and N-,N-2 hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and 3-hydroxyisobutyl. Aib is preferably unsubstituted. Aib is preferably αAib. ABU is preferably γABU or αγABU, more preferably α,γABU; and

X' is (1) $R_{1'}$-$R_{2'}$-Z, wherein $R_{1'}$ is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal, preferably $R_{1'}$ is DTrp, DαNal or DβNal, more preferably R_1 is DTrp or DαNal, and $R_{2'}$ is any natural L-amino acid, Pal, αNal, βNal, DpCl, Aib, preferably αAib, CHx where x is 1 to 10, or CHxAla, or any of their respective D-isomers, and Z is $CONH_2$ or COOH, preferably Z is $CONH_2$; or

(2) $R_{3'}$-$R_{4'}$, wherein $R_{3'}$ is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal, preferably $R_{3'}$ is DPro, DTrp, DαNal or DβNal, more preferably $R_{3'}$ is DPro, DTrp or DαNal, and $R_{4'}$ is

$NH(CH_2)_nNH$, where n is 1 to 8, such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide.

The organic and inorganic addition salts thereof are also included.

The abbreviations for the residues of amino acids used herein are in agreement with the standard nomenclature, and are set forth below:

Gly	Glycine
Tyr	L-Tyrosine
Ile	L-Isoleucine
Glu	L-Glutamic Acid
Thr	L-Threonine
Phe	L-Phenylalanine
Ala	L-Alanine
Lys	L-Lysine
Asp	L-Aspartic Acid
Cys	L-Cysteine
Arg	L-Arginine
Gln	L-Glutamine
Pro	L-Proline
Leu	L-Leucine
Met	L-Methionine
Ser	L-Serine
Asn	L-Asparagine
His	L-Histidine
Trp	L-Tryptophan
Val	L-Valine
Orn	L-Ornithine

Moreover, all of the three letter-abbreviations of the amino acids preceded by a "D" indicate the dextro-isomer of the aminoacidic residue, and glycine is considered to be included in the term naturally occurring L-amino acids. Other abbreviations used herein include the following:

Aib	aminoisobutyric acid
inip	isonipecotyl

ABU	aminobutyric acid
αNal	α-naphthyl alanine
βNal	β-naphthyl alanine
DαNal	α-naphthyl-D-alanine
DβNal	β-naphthyl-D-alanine
Pal	3-pyridyl alanine
CHx	cyclohexyl
CHxAla	L-cyclohexylalanine
Ava	Aminovaleric acid
IMA	Nα-imidazole acetic acid
IMC	imidazole carboxylic acid
βAla	β-Alanine

In one embodiment of the present invention, a group of preferred compounds includes:

γABUDTrpDTrpArgCOOH

α,γ ABUDTrpDTrpArgNH_2

α,γ ABUDTrpDTrpOrnNH_2

α,γ ABUDαNalDTrpLysNH_2

α,γ ABUDαNalDTrpArgNH_2

α,γ AbuDαNalDTrpArgNH_2

αAibDTrpDTrpArgNH_2

αAibDαNalDTrpArgNH_2

αAibDTrpDTrpArgCOOH

αAibDαNalDTrpArgCOOH

αAibDαTrpDTrpArgNH_2

αAibDTrpDPheArgNH_2

inipDαNalDTrpPheNH_2

inipDαNalDTrpCHxAlaNH_2

inipDαNalDTrpPheCOOH

inipDαNalDTrpPalNH_2

inipDαNalDTrpThrNH_2

inipDαNalDTrpValNH_2

inipDαNalDβNalPheNH$_2$

inipDαNalDTrpPheCOOH

inipDβNalDTrpPheNH$_2$

αAibDTrpDProGlyNH$_2$

αAibDTrpDProPheNH$_2$

αAibDTrpDProProNH$_2$

αAibDTrpDProDProNH$_2$

αAibDTrpDProDPheNH$_2$

αAibDTrpDProDPalNH$_2$

αAibDTrpDProDTrpNH$_2$

αAibDTrpDProDLeuNH$_2$

αAibDTrpDProDHisNH$_2$

αAibDTrpDProDValNH$_2$

αAibDTrpDProGlnNH$_2$

αAibDTrpDProArgNH$_2$

αAibDTrpDProLysNH$_2$

αAibDTrpDProDAlaNH$_2$

inipDαNalDpClPhePheNH$_2$

inipDαNalDpClPheArgNH$_2$

inipDαNalDTrpDProNH$_2$

αAibDTrpDProDSerNH$_2$

αAibDTrpDProDThrNH$_2$ and

αAibDTrpDProDIleNH$_2$.

In another embodiment of the present invention, a group of preferred compounds includes:

inipDTrpDTrpPheLysNH$_2$

inipDβNalDTrpPheLysNH$_2$

γABUDβNalDTrpPheLysNH$_2$

α,γABUDTrpDTrpPheLysNH$_2$

βAlaDTrpDTrpPheLysNH$_2$

α,γABUDβNalDTrpPheLysNH$_2$

α,γABUDTrpDTrpPheArg NH$_2$

α,γABUDαNalDTrpPheArgNH$_2$

inipDβBNalDTrpPheLysNH$_2$

inipDTrpDTrpPheArgNH$_2$

βAlaDαNalDTrpPheArgNH$_2$

αAibDTrpDTrpPheArgNH$_2$

αAibDTrpDTrpPheArgCOOH

inipDTrpDTrpPheArgCOOH

inipDαNalDTrpPheArg NH$_2$

inipDαNalDTrpPheArgCOOH

inipDαNalDβNalPheArgNH$_2$

inipDαNalDTrpPheDSerNH$_2$

inipDαNalDTrpPheDThrNH$_2$

inipDαNalDTrpPheGlyNH$_2$

inipDαNalDTrpPheGlnNH$_2$

inipDαNalDTrpPheDGlnNH$_2$

αAibDαNalDTrpPheGlnNH$_2$

inipDαNalDTrpPheDHisNH$_2$

αAibDTrpDProPheArgNH$_2$

αAibDTrpDProPheDArgNH$_2$

αAibDTrpDProDValArgNH$_2$

αAibDTrpDProDValDLysNH$_2$

αAibDTrpDProDValDArgNH$_2$

αAibDTrpDProDProArgNH$_2$

αAibDTrpDProDProDPalNH$_2$

αAibDTrpDProDProDArgNH$_2$

αAibDTrpDProDIleDArgNH$_2$

αAibDTrpDProDIleArgNH$_2$

αAibDTrpDProDProDLysNH$_2$ and

αAibDTrpDProIleArgNH$_2$.

In the above Formula I, where X is R_5-R_6 and R_6 is a C(=0) (substituted heteroalicyclic or heteroaromatic), the heteroatom is selected from the group consisting of O, N, S and P.

The heteroalicyclic moiety preferably contains 2 to 12 carbon atoms, more preferably 3 to 8 carbon atoms. The heteroaromatic moiety preferably contains 5 to 12 carbon atoms, more preferably 5 to 11 carbon atoms. Substituents include NH_2, C_1-C_{12} lower alkyl, and as listed below.

Examples include piperidine-3-methyl-benzylether, N-diethylnipectamide, N-piperazine methylsulfonamide, diethylamide, m-methylpiperidine, 3,3-diphenylpropylamide, 4-piperidino piperidinamide, 4-phenyl-piperidinamide, N-methyl 1-piperiazine, 2-morpholinoethylamine, spiroindole methylsulfonamide, pyrrolidine amide, indoleamide, 3-piperidine methanol amide, tropin amide, 2-aminoethylamide, 3-aminopropylamide, 4-aminobutylamide, 5-aminopentylamide, 6-aminohexylamide. Preferred substituted heteralicyclic or heteroaromatic include N-diethylnipectamide, piperidine-3-methyl-benzylether, N-piperazine methyl sulfonamide, diethylamide and m-methylpiperidine. Even more preferred are N-diethylnipectamide and piperidine-3-methyl-benzylether.

Preferably, the compound has the structure AibDTrpX, where X is $DProNH_2$, DPro-diisobutylamide, DProbutylamide, DPro-C(=0)(substituted heteroalicyclic or heteroaromatic), and DTrp-Phe-Arg-5-aminopentamide and organic and inorganic addition salts thereof. More preferably, X is DPro-diisobutylamide, DPro-C(=0)(substituted heteroalicyclic or heteroaromatic) and DTrp PheArg-5-aminopentamide, and organic and inorganic addition salts thereof. Still more preferably, X is DPro-diisobutylamide or DTrp-Phe-Arg-5-aminopentamide, and organic and inorganic addition salts thereof. Even more preferably, X is DPro-diisobutylamide and organic and inorganic addition salts thereof.

In an alternative embodiment the compound has the formula

$$A_1\text{-}Y,$$

wherein A_1- is Aib, inip, ABU, βAla, His, Sar or any of their respective D-isomers. The Aib residue can be substituted or unsubstituted. Preferred substituents include N- and N-, N-C_1-C_6 alkyl, halogens, N- and N-, N-2 hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and 3-hydroxyisobutyl. Aib is preferably unsubstituted. A_1- is preferably Aib, inip or ABU. More preferably Aib is αAib. Abu is preferably γAbu or α,γAbu, more preferably α,γAbu.

Y is $A_{2'}$-A_3-A_4-A_5-A_6-Z',

$A_{2'}$-A_3-A_4-A_5-Z' or $A_{2'}$-A_3-A_4-Z'

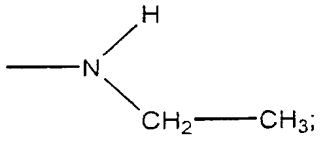
wherein $A_{2'}$ is A_5-$A_{2''}$ or $A_{2''}$,

wherein A_5 is a spacer amino acid such as His,

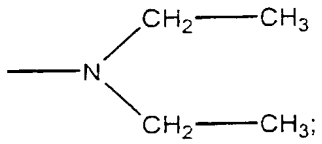
$A_{2''}$ is as defined above for A_2. $A_{2''}$ is preferably DTrp, DαNal or DβNal. $A_{2''}$ is more preferably DTrp.

A3, A4 and A5 are any natural L-amino acid, Pal, αNal, βNal, Nle, Arg-DPro, DPCl, D or L (CHX), cyclohexylalanine (CHXAla), or any of their respective D-isomers, preferably A_3 is DPro, DTrp, DβNal or DPhe, more preferably A_3 is DPro or DTrp; and A_4 is preferably Gly, Phe, Pro, Ile, DPro, DPhe, DPal, DLeu, DHis, DVal, DGln, DIle, DNle, DArg, DAla, DSer, DThr, DIle, Arg, Orn Lys, Ala, Pal, Thr, Val, PheCHX, CHXAla or CHX. A_4 is preferably DSer, DAug, DPro, DTrp, DVal, DIle, DThr, DNVal, DNle, Ile, Pro, Phe and still more preferably, A_4 is DPro. A_5 is preferably Ile, Arg, Pal, DArg, DSer, Lys and Arg-DPro. More preferably A_5 is Arg, DArg, and Lys.

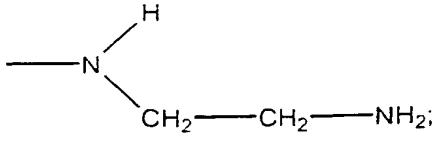
Z' is NH_2, OH or (aminoalkyl) or (aminoalkylamino), preferably the aminoalkyl is NH (C_1-C_{10} alkyl) e.g. $NH(CH_2)_nCH_3$, where n is 1 to 10 such as



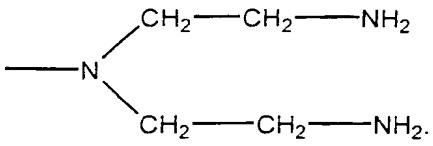
N di-(C_1-C_{10} alkyl) e.g., N di-$(CH_2)_n$ CH_3 such as



preferably the alkylamino is a NH (C_1-C_{10} alkylamino, e.g. $NH(CH_2)_nNH_2$ such as



N (di C_1-C_{10} alkylamino), e.g., N [di-$(CH_2)_nNH_2$] such as



Preferred examples include moieties such as -2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, or -6-aminohexylamide; N-dimethylamide; N-diethylamide; N-dipropylamide; N-dibutylamide; N-diisobutylamide; N-dipentylamide; N-dihexylamide;

A particularly preferred embodiment is Aib-Y, more preferably αAib-Y.

Y is preferably $A_{2''}$-DPro-A_4-A_5-A_6-Z'; $A_{2''}$-A_3-A_4-Z'; or $A_{2''}$-A_3-A_4-A_5-Z'. Y is more preferably $A_{2''}$-DPro-A_4-Z' or $A_{2''}$-DPro-A_4-Z' or $A_{2''}$-DPro-A_4-A_5-Z'. Still more preferably Y is $A_{2''}$-DPro-A_4-A_5-Z'. Z' is preferably $-NH_2$.

Preferred embodiments include

αAib-DTrp-DPro-A_4-A_5-A_6-Z';

αAib-DTrp-DPro-A_4-A_5-Z';

αAib-DTrp-DPro-A_4-Z';

αAib-DTrp-DPro-A_4-Arg-NH_2;

αAib-DTrp-DPro-A_4-Arg-A_6-NH_2;

αAib-DTrp-DPro-A_4-Arg-Gly-NH_2;

αAib-DαNal-DPro-A_4-A_5-A_6-Z';

αAib-DαNal-DPro-A_4-A_5-Z';

αAib-DαNal-DPro-A_4-Z';'

αAib-DαNal-DPro-A_4-NH_2;

αAib-DαNal-DPro-A_4-Arg-NH_2;

and αAib-DαNal-DPro-A_4-Arg-Gly-NH_2.

A_4 is preferably DIle, DThr, DNle, DVal, DGln, DAla, DPhe, DTrp, DNVal and Arg.

Exemplery representatives of αAib-$A_{2''}$-DPro-A_4-Arg-Z' include

αAibDTrpDProDIleArgNH_2;

αAibDTrpDProDThrArgNH$_2$;

αAibDTrpDProDValArgNH$_2$;

αAibDTrpDProDNleArgNH$_2$; and

αAibDαNalDProDIleDArgNH$_2$.

Exemplary representatives of:

αAib-A$_{2''}$-DPro-A$_4$-Z include

αAib-DTrp-DPro-DThr-NH$_2$;

αAib-DTrp-DPro-DGln-NH$_2$;

αAib-DTrp-DPro-Arg-NH$_2$;

αAib-DTrp-DPro-DAla-NH$_2$;

αAib-DTrp-DPro-DPhe-NH$_2$;

αAib-DTrp-DPro-DTrp-NH$_2$;

αAib-DTrp-DPro-DVal-NH$_2$;

αAib-DTrp-DPro-DNVal-NH$_2$; and

αAib-DTrp-DPro-DIle-NH$_2$;

Exemplary representatives of αAib-A$_{2''}$-DPro-A$_4$-Arg-A$_6$-Z include compounds of the formula αAib-A$_{2''}$-DPro-A$_4$-Arg-Gly-NH$_2$ such as

αAib-DTrp-DPro-DIle-Arg-Gly-NH$_2$;

αAib-DTrp-DPro-DThr-Arg-Gly-NH$_2$; and

αAib-DTrp-DPro-DNle-Arg-Gly-NH$_2$.

Representative compounds are set forth below:

inipDαNalDTrpNH$_2$;

inipDαNalDValNH$_2$;

αAibDTrpDValNH$_2$;

αAibDTrpDProDSerNH$_2$;

αAibDTrpDProDArgNH$_2$;

αAibDTrpDProDPheNH$_2$;

αAibDTrpDProDTrpNH$_2$;

αAibDTrpDValDValNH$_2$;

αAibDValDProDValNH$_2$;

αAibDValDValDValNH$_2$;

αAibDTrpDProDLysNH$_2$;

αAibDProDProDValNH$_2$;
inipDαNalDTrpDValNH$_2$;
αAibDTrpDProIleNH$_2$;
αγAbuDαNalDTrpDIleNH$_2$;
inipDαNalDTrpDProIleNH$_2$;
inipDαNalDTrpPheIleNH$_2$;
inipDαNalDTrpDValArgNH$_2$;
αAibDTrpDProDValDValNH$_2$;
αAibDTrpDProDProDPalNH$_2$;
αAibDTrpDProDValArgDProNH$_2$;
αAibDTrpDProDIleDArgNH$_2$;
αγAbuDTrpDTrpDIleNH$_2$;
inipDαNalDTrpPheDValNH$_2$;
αAibDTrpDProValNH$_2$;
αAibDTrpDIleDIleNH$_2$;
αAibDTrpDProLeuNH$_2$;
αAibDTrpDProThrNH$_2$;
DHisDTrpDProDValArgNH$_2$;
DHisDTrpDProDThrNH$_2$;
αAibDTrpDProDIleNH$_2$;
αAibDTrpDPheDValNH$_2$;
αAibDTrpDProDValDArgNH$_2$;
αAibDTrpDProDAlaNH$_2$;
αAibDTrpDProDProNH$_2$;
αAibDTrpDProArgNH$_2$;
αAibDTrpDProDValNH$_2$
inipDαNalDTrpDProNH$_2$;
αAibDαNalDProDValDArgNH$_2$;
αAibDαNalDProDIleDArgNH$_2$;
αAibDTrpDProDProDLysNH$_2$;
αAibHisDαNalDPheLysNH$_2$;
αAibHisDTrpDProDValNH$_2$;

αAibHisDTrpDProDIleNH$_2$;
αAibHisDTrpDProValArgNH$_2$;
αAibHisDTrpDProDValArgNH$_2$;
αAibDαNalDProDValNH$_2$;
αAibDTrpDProDThrArgNH$_2$;
αAibDTrpDProDNleArgNH$_2$;
αAibDTrpDProDNValArgNH$_2$;
αAibDTrpDProIleArgNH$_2$;
αAibDTrpDProDProArgNH$_2$;
αAibDTrpDProProArgNH$_2$;
αAibDTrpDProDProDArgNH$_2$;
αAibDTrpDProDIleArgNH$_2$;
αAibDTrpDProPheDSerNH$_2$;
αAibDTrpDProPheArgNH$_2$;
αAibDTrpDProDValArgNH$_2$;
SarDTrpDTrpPheArgNH$_2$;
αAibDαNalDProDProArgNH$_2$;
αAibDαNalDProDNValArgNH$_2$;
αAibDαNalDProDIleArgNH$_2$;
αAibDαNalDProDValLysNH$_2$;
αAibDαNalDProDThrArgNH$_2$;
αAibDαNalDProDThrArgNH$_2$;
αAibDαNalDProDValArgNH$_2$;
αAibDαNalDProDValArgNH$_2$;
αAibDTrpDProDNleNH$_2$;
αAibDTrpDProDNValNH$_2$.
αAibDTrpDProDIle-X$_a$, where X$_a$ is
2-aminoethylamide,
5-aminopentylamide, or
3-aminopropylamide.
αAibDTrpDProDVal-X$_b$, where X$_b$ is
2-aminoethylamide,
dimethylamide, or

diethylamide.

αAibDTrpDProDPro-X_c, where X_c is

2-aminoethylamide.

The following compounds are preferred

αAibDTrpDProDIleXd, where X_d is

5-aminopentylamide,

3-aminopropylamide,

2-aminoethylamide, or

4-aminobutylamide

αAibDTrpDProDValX$_e$, where X_e is

N-dimethylamide,

N-diethylamide, or

2-aminoethylamide;

αAibDTrpDProDValX$_f$, where X_f is

5-aminopentylamide;

αAibDTrpDProDNleX$_g$, where X_g is

5-aminopentylamide;

αAibDTrpDProDProArgNH_2;

αAibDTrpDProDValDArgNH_2;

αAibDTrpDProDValArgNH_2;

αAibDTrpDProDIleArgNH_2;

αAibDαNalDProDValArgNH_2;

αAibDαNalDProDValArgNH_2;

αAibDαNalDProDIleArgNH_2;

αAibDαNalDProDValLysNH_2;

inipDαNalDαNalPheArgNH_2;

αAibDTrpDProDThrArgNH_2;

αAibDTrDProDNleArgNH_2;

αAibDTrpDProDNValArgNH_2;

αAibDTrpDProDIleArgGlyNH_2;

αAibDTrpDProDProDIleArgGlyNH_2;

αAibDTprDProDNleArgGlyNH_2; and

αAibDTrpDProDThrArgGlyNH_2;

In one embodiment one uses compound from compounds having the formula

αAibDTrpDProDProA$_4$ArgNH$_2$ or

αAibDTrpDProDProA$_4$ArgGlyNH$_2$.

Preferred examples are selected from the group consisting of

αAibDTrpDProDIleArgNH$_2$

αAibDTrpDProDIleArgGlyNH$_2$

αAibDTrpDProDProDIleArgNH$_2$, and

αAibDTrpDProDProDIleArgGlyNH$_2$.

In an alternate embodiment, the following peptides are of interest:

DβNalAlaTrpDPheLysGlnGlyNH$_2$

DAlaDTrpAlaTrpDPheLysValGlyNH$_2$

DAlaDβNalAlaTrpDPheLysGlnGlyGlyGlyNH$_2$

DAlaDTrpAlaTrpDPheLysHisGlyNH$_2$

These secretagogues can be used therapeutically for any use for which growth hormone can be used, such as treating hypothalamic pituitary dwarfism, osteoporosis, burns, and renal failure for acute use, for non-union bone fracture, and to promote wound healing. Additionally, it can be used to promote recovery from surgery, and acute/chronic debilitating medical illnesses. Beneficial anabolic effects result on skin, muscle and bone in relation to the aging process with a concomitant decrease in body fat. Treatment of cancer patients by these peptides is also included, for example, prevention and/or reduction of cachexia in cancer patients. These therapeutic uses are accomplished by using a therapeutically effective amount of the compound. Such an amount is that needed to promote the release of serum growth hormone levels as discussed, infra.

The compounds of this invention may also be used to enhance blood GH levels in animals; enhance milk production in cows; enhance body growth in animals such as, e.g., humans, sheep, bovines, and swine, as well as fish, fowl, other vertebrates and crustaceans; and increase wool and/or fur production in mammals. The amount of body growth is dependent upon the sex and age of the animal species, quantity and identity of the growth

hormone releasing compound being administered, route of administration, and the like.

Also, the compounds of this invention increase serum GH in humans; enhance body growth in short stature children; decrease body fat and improve protein metabolism in select children; improve protein metabolism of the skin, muscle, bone while decreasing body fat of the elderly, particularly when GH deficiency is present.

These compounds are also useful for improving serum lipid pattern in humans by decreasing in the serum the amount of serum cholesterol and low density lipoprotein, and increasing in the serum the amount of the high density lipoprotein.

The novel secretagogues of this invention can be synthesized according to the usual methods of solution and solid phase peptide chemistry, or by classical methods known in the art.

In accordance with another embodiment of the present invention, a method is provided for promoting release and/or elevation of growth hormone levels in the blood of an animal. This method of promoting the release and/or elevation of growth hormone levels can also be used to therapeutically treat the aforesaid diseases. Said methods comprise administering to an animal an effective dose of at least one of the above-described compounds. In one embodiment, this method is used in animals other than humans.

The compounds of this invention can be administered by oral, parenteral (intramuscular (i.m.), intraperitoneal (i.p.), intravenous (i.v.) or subcutaneous (s.c.) injection), nasal, vaginal, rectal or sublingual routes of administration as well as intrapulmonary inhalation can be formulated in dose forms appropriate for each route of administration. Parenteral administration is preferred.

Solid dose forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dose forms, the active compound is mixed with at least one inert carrier such as sucrose, lactose, or starch. Such dose forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dose

forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dose forms for oral administration include emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides, such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dose forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in a medicum of sterile water, or some other sterile injectable medium immediately before use.

The amount of secretagogues or combination of compounds of the present invention administered will vary depending on numerous factors, e.g., the particular animal treated, its age and sex, the desired therapeutic affect, the route of administration and which polypeptide or combination of polypeptides are employed. In all instances, however, a dose effective (therapeutically effective amount) to promote release and elevation of growth hormone level in the blood of the recipient animal is used. Ordinarily, this dose level falls in the range of between about 0.1μg to 10mg of total compound per kg of body weight. The preferred amount can readily be determined empirically by the skilled artisan based upon the present disclosure.

For example, in humans when the mode of administration is i.v. the preferred dose level falls in the range of about 0.1μg to 10μg of total secretagogue per kg of body weight, more preferably, about 0.5μg to 5μg of total secretagogue per kg of body weight, still more preferably about 0.7 μg

about 3.0μg per kg of body weight. When combinations of growth hormone releasing compounds are used, lower amounts of the presently described peptide can be used. For example, combining the presently described secretagogues with, for example, a synergistic compound in Group I of U.S. Patent No. 4,880,778 such as GHRH, or U.S. Patent No. 5,663,146 or 5,486,505, a preferred range is about 0.1μg to about 5μg of the presently described compound per kg of body weight and about 0.5μg to about 15.0μg of synergistic compound (e.g. GHRH) and more preferably about 0.1μg to about 3μg of the present compound with about 1.0μg to about 3.0μg of the synergistic compound per kg of body weight.

When the mode of administration is oral, greater amounts are typically needed. For example, in humans for oral administration, the dose level is typically about 30μg to about 1200μg of compound per kg of body weight, more preferably about 70μg to about 600μg of compound per kg of body weight, still more preferably, about 200μg to about 600μg of total compound per kg of body weight. Cows and pigs require about the same dose level as humans, while rats typically require higher dose levels. The exact level can readily be determined empirically based upon the present disclosure.

In general, as aforesaid, the administration of combinations of growth hormone releasing peptides will allow for lower doses of the individual growth hormone releasing compounds to be employed relative to the dose levels required for individual growth hormone releasing compounds in order to obtain a similar response, due to the synergistic effect of the combination.

Also included within the scope of the present invention are compositions that comprise, as an active ingredient, the organic and inorganic addition salts of the above-described polypeptides and combinations thereof; optionally, in association with a carrier, diluent, slow release matrix, or coating.

The organic or inorganic addition salts of the growth hormone releasing compounds and combinations thereof contemplated to be within the scope of the present invention include salts of such organic moieties as acetate, trifluoroacetate, oxalate, valerate, oleate, laurate, benzoate, lactate,

tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthalate, and the like; and such inorganic moieties as Group I (i.e., alkali metal salts), Group II (i.e. alkaline earth metal salts) ammonium and protamine salts, zinc, iron, and the like with counterions such as chloride, bromide, sulfate, phosphate and the like, as well as the organic moieties referred to above.

Pharmaceutically acceptable salts are preferred when administration to human subjects is contemplated. Such salts include the non-toxic alkali metal, alkaline earth metal and ammonium salts commonly used in the pharmaceutical industry including sodium, potassium, lithium, calcium, magnesium, barium, ammonium and protamine salts which are prepared by methods well known in the art. The term also includes non-toxic acid addition salts which are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. Representative salts include hydrochloride, hydrobromide, sulfate, bisulfate, acetate, oxalate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate and the like.

The invention will be further illustrated by the following non-limiting examples.

EXAMPLES OF THE INVENTION

The following examples are designed to illustrate certain aspects of the present invention. The examples are not intended to be comprehensive of all features and all embodiments of the present invention, and should not be construed as limiting the claims presented herein.

General Methods for Synthesis

1H NMR spectra were measured ($SiMe_4$ internal standard) on a GE-500 (500 MHz) Spectrometer. Mass spectra data were obtained by using a "Lasermat" Laser Desorption Mass Spectrometry. Reagents were obtained from commercial sources and used without further purification. Solvents were dried according to standard procedures. Scheme 1 can be utilized for additions with any amine group recorded in Table 1.

Example 1

Synthesis of the Growth Hormone Releasing Peptides

Paramethyl benzhydrylamine hydrochloride (pMe-BHA HCl) resin is placed in a reaction vessel on a commercially available automated peptide synthesizer. The resin is substituted with free amine up to a loading of about 5 mmoles per gram. The compounds are prepared by coupling individual amino acids starting at the carboxy terminus of the peptide sequence using an appropriate activating agent, such as N,N' dicyclohexylcarbodiimide (DCC). The alpha amine of individual amino acids are protected, for example, as the t-butyloxycarbonyl derivative (t-Boc) and the reactive side chain functionalities are protected as outlined in Table 1.

Table 1

Side Chain Protecting Groups Suitable for Solid Phase Peptide Synthesis

Arginine	N^g—Tosyl
Aspartic Acid	O-Benzyl
Cysteine	S-para-Methylbenzyl
Glutamic Acid	O-Benzyl
Histidine	N^{im}-Tosyl
Lysine	N^{ϵ} –2,4-Dichlorobenzyloxycarbonyl
Methionine	S-Sulfoxide
Serine	O-Benzyl
Threonine	O-Benzyl
Tryptophan	N^{in}-Formyl
Tyrosine	O-2,6-Dichlorobenzyl

Prior to incorporation of the initial amino acid, the resin is agitated three times (about one minute each) with dichloromethane (CH_2C_{12}: about 10 ml/gm of resin), neutralized with three agitations (about two minutes each) of N,N-diisopropylethylamine (DIEA) in dichloromethane (10:90; about 10 ml/gm of resin) and agitated three times (about one minute each) with dichloromethane (about 10 mL/gm of resin). The initial and each of the subsequent amino acids are coupled to the resin using a preformed symmetrical anhydride using about 6.0 times the total amount of the reaction capacity of the resin of a suitably protected amino acid and about 2.0 times the total amount of the binding capacity of the resin of DIC in an

appropriate amount of dichloromethane. For amino acids with a low dichloromethane solubility, N,N-dimethylformamide (DMF) is added to achieve a homogenous solution. Generally, the symmetrical anhydride is prepared up to 30 minutes prior to introduction into the reaction vessel at room temperature or below. The dicyclohexylurea that forms upon preparation of the symmetrical anhydride is removed via gravity filtration of the solution into the reaction vessel. Progress of the coupling of the amino acid to the resin is commonly monitored via a color test using a reagent such as ninhydrin (which reacts with primary and secondary amines). Upon complete coupling of the protected amino acid to the resin (>99%), the alpha amine protecting group is removed by treatment with acidic reagent(s). A commonly used reagent consists of a solution of trifluororacetic acid (TFA) in dichloromethane (33:66).

After the desired amino acid sequence has been completed, the desired peptide can be cleaved from the resin support by treatment with a reagent such as hydrogen fluoride (HF) which not only cleaves the peptide from the resin, but also cleaves most commonly used side-chain protecting groups. When the BHA or p-Me-BHA resin is used, HF treatment results directly in free peptide amides. When an amino acid-Merrifield resin is used, free peptide alkylamides are cleaved by treatment with an appropriate amine (in this case, use of Boc-N^{ϵ}-FMOC-Lys would allow simultaneous removal of the FMOC group).

The complete procedure for incorporation of each individual amino acid residue onto the resin is outlined in Table 2.

Table 2

Procedure for Incorporation of Individual Amino Acids onto a Resin

	Reagent	Agitations	Time/Agitation
1.	Dichloromethane	3	1 min.
2.	TFA-Dichloromethane (33:66)	1	2 min.
3.	TFA-Dichloromethane (33:66)	1	20 min.
4.	Dichloromethane	3	1 min.
5.	DIEA, DMF (10:90)	2	2 min.
6.	Dichloromethane	3	1 min.
7.	Boc amino acid/DIC	1	15-120 min *
8.	Dichloromethane	3	1 min.
10.	Monitor progress of the coupling reaction **		
11.	Repeat steps 1-12 for each individual amino acid		

* Coupling time depends upon the individual amino acid.

** The extent of coupling can be generally monitored by a color test. If the coupling is incomplete, the same amino acid can be recoupled by a different protocol, e.g. HOBt active ester. If the coupling is complete the next amino acid can then be coupled.

Using this procedure the compounds described in Tables 3, 4 and 5 were made.

Example 2

In Vivo GH Release in Rats

Immature female Sprague-Dawley rats were obtained from the Charles River Laboratories (Wilmington, MA). After arrival they were housed at 25°C with a 14:10 hour light:dark cycle. Water and Purina rat chow were available *ad libitum*. Pups were kept with their mothers until 21 days of age.

Twenty-six day old rats, six rats per treatment group, were anesthetized interperitoneally with 50 mg/kg of pentobarbital 20 minutes prior to i.v. treatment with peptide. Normal saline with 0.1% gelatin was the vehicle for intravenous (i.v.) injections of the peptides. The anesthetized rats, weighing 55-65 grams, were injected i.v. with the quantity of grown hormone releasing compounds indicated in Table 3. Injection was made as a 0.1 mL solution into the jugular vein.

All animals were sacrificed by guillotine 10 minutes after final test injection (see Table 3). Trunk blood for the determination of blood GH levels was collected following decapitation. After allowing the blood to clot, it was centrifuged and the serum was separated from the clot. Serum was kept frozen until the day of sampling for radioimmunoassay (RIA) determination of growth hormone levels according to the following procedure, as developed by the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDK).

Reagents are generally added to the RIA analysis tubes at a single sitting, at refrigerator temperature (about 4°C) in the following sequence:

(a) buffer,

(b) "cold" (i.e., non-radioactive) standard or unknown serum sample to be analyzed,

(c) radio-iodinated growth hormone antigen, and

(d) growth hormone antiserum.

Reagent addition is generally carried out so that there is achieved a final RIA tube dilution of about 1:30,000 (antiserum to total liquid volume; vol:vol).

The mixed reagents are then typically incubated at room temperature (about 25°C) for about 24 hours prior to addition of a second antibody (e.g., goat or rabbit anti-monkey gamma globulin serum) which binds to and causes precipitation of the complexed growth hormone antiserum. Precipitated contents of the RIA tubes are then analyzed for the number of counts in a specified period of time in a gamma scintillation counter. A standard curve is prepared by plotting number of radioactive counts versus growth hormone (GH) level. GH levels of unknown are then determined by reference to the standard curve.

Serum GH was measured by RIA with reagents provided by the National Hormone and Pituitary Program.

Serum levels in Tables 3 and 4 are recorded in ng/mL in terms of the rat GH standard of 0.61 International Units/mg (IU/mg). Data is recorded as the mean ± standard error of the mean (SEM). Statistical analysis was performed with Student's t-test. In Table 3, the results shown are the average of studies with six rats.

Example 3

Synthesis of Aib-DTrp-DPro-diisobutylamide (YL-156)

(1) Synthesis of DPro-Diisobutylamide (1):

1 mmol of Boc-DPro (Boc=tert-Butoxycarbonyl group) was dissolved in 30 ml dry CH_2Cl_2 in a 100 ml round bottom flask, with 1 mmol of 1-hydroxybenzotriazole added while stirring under N_2 atmosphere in an ice-bath, then 1.05 mmol of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide HCl was added in 10 ml dry CH_2Cl_2 at a fast drop rate and the reaction mixture was stirred for 1 hour at 0° C. 1.1 mmol of diisobutylamine in 10 ml of CH_2Cl_2 was added dropwise and stirring was continued for a further 18 h at ambient temperature. The reaction mixture was washed with 20 ml of 20% aqueous citric acid, 20 ml of saturated aqueous $NaHCO_3$, and 20 ml of saturated aqueous sodium chloride. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum. Further purification was done by flash column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5) to afford white solid of Boc-DPro-diisobutylamide.

Under N_2 atmosphere, the Boc-DPro-diisobutylamide was dissolved in 25 ml of CH_2Cl_2 and 1- ml of trifluoracetic acid was added while being stirred. The reaction mixture was stirred for 30 min. Volatiles were removed under vacuum and the residue was dissolved in 30 ml of CH_2Cl_2 and washed with 10 ml saturated $NaHCO_3$ aqueous solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and filtered and the solvent was removed in vacuum. The residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 85:15) to afford 0.73 mmol

(73%) of compound (1) which was characterized by TLC on mass spectra, M^+=225.1.

(2) Synthesis of DTrp-DPro-diisobutylamide (2):

In a 100 ml round bottom flask, 0.70 mmol of Boc-DTrp was dissolved in 25 ml dry CH_2Cl_2 and 0.70 mmol of 1-hydroxybenzotriazole was added while stirring under N_2 atmosphere in an ice-bath then 0.75 mmol of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide HCl was added in 15 ml dry CH_2Cl_2 at a fast drop rate and the reaction mixture stirred for 1 hour at 0°C. 0.71 mmol of (1) in 20 ml of CH_2Cl_2 was added dropwise and stirring was continued for a further 18 h at ambient temperature. The reaction mixture was washed with 20 ml of 20% citric acid aqueous solution, 20 ml of saturated $NaHCO_3$ aqueous solution, and 20 ml of saturated sodium chloride aqueous solution. The organic layer was separated and dried over anhydrous magnesium sulfate, filters and concentrated by vacuum. Further purification was done by flash column chromatography ($CHCl_3$/MeOH, 95:5) to afford white solid of Boc-DTrp-D-diisobutylamide.

Under N_2 atmosphere, the Boc-DTrp-DPro-diisobutylamide was dissolved in 25 ml of CH_2Cl_2, 1 ml of methylsulfide and 0.5 ml of 1,2-ethanedithiol was added as scavenger in suppressing the indole alkylation of tryptophane. 10 ml of trifluoracetic acid was added dropwise while being stirred. The reaction mixture was stirred for 30 min. Volatiles were removed under vacuum and the residue was dissolved in 30 ml of CH_2Cl_2 and washed with 10 ml saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous sodium sulfate and filtered and the solvents were removed in vacuum. The residue was further purified by column chromatography (SiO_2, $CHCl_2$/MeOH, 85:15) to afford 0.55 mmol (78.5%) of compound (2) which was characterized by TLC and mass spectra, M^+=411.5.

(3) Synthesis of Aib-DTrp-DPro-diisobutylamide (YL-156):

In a 100 ml round bottom flask, 0.50 mmol of Boc-Aib (Aib=α-aminoisobutyric acid) was dissolved in 30 ml dry CH_2Cl_2 and then 0.51 mmol of 1-hydroxybenzotrizole was added while stirring under N_2 atmosphere in an ice-bath, 0.55 mmol of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide HCl was added in 20ml dry CH_2Cl_2 at a fast drop rate and the reaction was stirred for 1 hour at 0° C. 0.51 mmol of (2) in 15 ml of CH_2Cl_2

was added dropwise and stirring was continued for a further 18 h at ambient temperature. The reaction mixture was washed with 20 ml of 20% citric acid aqueous solution, 20 ml of saturated $NaCHO_3$ aqueous solution, and 20 ml of saturated sodium chloride aqueous solution. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum. Further purification was done by flash column chromatography ($CHCl_3$/MeOH, 95:5) to afford white solid of Boc-Aib-DTrp-DPro-diisobutylamide.

Under N_2 atmosphere, the Boc-Aib-DTrp-DPro-diisobutylamide was dissolved in 30 ml of CH_2Cl_2, 1 ml of methylsulfide and 0.5 ml of 1,2-ethanedithiol were added as scavengers to suppress the indole alkylation of tryptophan. 10 ml of trifluoracetic acid was added dropwise while being stirred. The reaction mixture was stirred for 30 min. Volatiles were removed under vacuum and the residue was dissolved in 30 ml of CH_2Cl_2 and washed with 10 ml saturated $NaHCO_3$ aqueous solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate, and filtered and the solvents were removed in vacuum. The residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 85:15) to afford 0.43 mmol (86.2%) of compound (YL-156) which was characterized by TLC and mass spectra M^+=497.6.

Example 4

Synthesis of inip-DαNal-DTrp-Phe-2-aminoethylamide (YL-105)

3.5 g of Wang resin with the peptide attached was supplied by Research Genetics Laboratory. It was added to a 100 ml round-bottom flask and then sequentially 40 ml of dry CH_2Cl_2, 4 ml of methanol and 2 ml of 1,2-diaminoethane were added while stirring under N_2 atmosphere. The reaction mixture was stirred for 72 hours at RT. The reaction mixture was filtered and the resin was washed with 20 ml of dry CH_2Cl_2, 20 ml of methanol. The solid resin was discarded. The organic solvent was removed by vacuum. The solid residue was further purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5) to afford white solid of YL-105.

Further purification was performed by preparative HPLC. Molecular weight was determined by MS.

Example 5

Synthesis of (N-2-hydroxylethyl-Aib-DTrp-DPro-diisobutylamide (YL-185) (Reductive Alkylation)

1 mmol of YL-156 (αAibDTrpDPro-diisobutylamide)was dissolved in 40 ml dry methanol in a 100 ml round-bottom flask and 1.5 mmol of $NaBH_4$ in THF was added while stirring under N_2 atmosphere. The solution was acidified by adding trifluoracetic acid in methanol to adjust the pH to 6.5. Then 1.15 mmol of ethylaldehyde was added in 10 ml dry methanol and the reaction mixture was stirred for 16 hours at RT. The solvent was removed by vacuum. The remaining residue was dissolved in 30 ml CH_2Cl_2 and washed with 20 ml of saturated aqueous $NaHCO_3$. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuum. Further purification was done by flash column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5) to afford white solid of YL-185.

Further purification was performed by preparative HPLC. The molecular weight was determined by MS.

Example 6

Synthesis of (N-isobutyl)Aib-DTrp-DPro-diisobutylamide (YL-194) (Hoffman Alkylation)

1 mmol of YL-156 (αAibDTrpDPro-diisobutylamide) was dissolved in 40 ml dry CH_2Cl_2 in a 100 ml round-bottom flask. 2 mmol of K_2CO_3 was then added while stirring under N_2 atmosphere. 1.15 mmol of 1-bromo-2-methylpropane was added in 10 ml dry CH_2Cl_2 and the reaction mixture stirred for 72 hours at RT. The reaction mixture was washed with 20 ml of saturated aqueous $NaHCO_3$ and 20 ml of saturated aqueous sodium chloride. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. Further purification was done by flash column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5) to afford white solid of YL-194.

Further purification was performed by preparative HPLC. Molecular weight was determined by MS.

Example 7

Synthesis of Aib-DTrp-DTrp-Phe-Arg-5-aminopentylamide (YL-174)

0.7 mmol of Fmoc-Aib-DTrp-DTrp-Phe-ArgCOOH was synthesized by Research Genetics Laboratory by the solid phase method and added to a 100 ml round-bottom flask with 40 ml of dry CH_2Cl_2. 0.70 mmol of 1-hydroxybenzotriazole was added while stirring under N_2 atmosphere in an ice-bath and subsequently 0.75 mmol of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide HCl was added in 15 ml dry CH_2Cl_2 at a fast drop rate. The reaction mixture was stirred for 1 hour at 0°C. 10 mmol of 1,5-diaminopentane in 20 ml of CH_2Cl_2 was added quickly and stirring was continued for an additional 18 h at ambient temperature. The reaction mixture was washed with 20 ml of saturated $NaHCO_3$ aqueous solution and 10 ml of saturated sodium chloride aqueous solution. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. Further purification was done by flash column chromatography ($CHCl_3$/MeOH, 95:5) to afford white solid of Fmoc-Aib-DTrp-DTrp-Phen-ArgCONH$(CH_2)_5NH_2$. This compound was dissolved in 20 ml of CH_2Cl_2 and under N_2 atmosphere 10 ml of piperidine was added. The solution was stirred for another 4 hours. The solvent was removed by vacuum and the residue was further purified by flash column chromatography ($CHCl_3$/MeOH, 95:5) to afford white solid of YL-174.

Further purification was performed by preparative HPLC. Molecular weight was determined by MS.

Example 8

Synthesis of Aib-DTrp-DPro-3-methylpiperidinamide (YL-111)

(Aib-DTrp-DPro-R, R=various of amine end groups, for example piperidine, 3-methyl piperidine, etc. All other Aib-DTrp-DPro-R compounds can be synthesized by using the same procedure):

(1) Synthesis of DPro-3-methylpiperidinamide (methylpiperidine) (1):

1 mmol of Boc-DPro (Boc=tert-Butoxycarbonyl group) was dissolved in 30 ml dry CH_2Cl_2 in a 100 ml round-bottom flask, 1 mmol of 1-hydroxybenzotriozole added while stirring under N_2 atmosphere in an ice-bath, 1.05 mmol of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide HCL was added in 10 ml dry CH_2Cl_2 at a fast drop rate and the reaction mixture stirred for 1 hour at 0° C. 1.1 mmol of 3-methylpiperazine in 10 ml of CH_2Cl_2 was added dropwise and stirring was continued for an additional 18 h at ambient temperature. The reaction mixture was washed with 30 ml of 20% aqueous citric acid, 30 ml of saturated aqueous $NaHCO_3$, and 30 ml of saturated aqueous sodium chloride. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuum. Further purification was done by flash column chromatography (SiO_2, $CHCl_3$/MeOH, 95:5) to afford white solid of Boc-DPro-D-piperidinamide.

Under N_2 atmosphere, the Boc-DPro-3-piperidinamide was dissolved in 25 ml of CH_2Cl_2 and 10 ml of trifluoracetic acid added while stirring. The reaction mixture was stirred for 30 min. All volatiles were removed under vacuum and the residue dissolved in 30 ml of CH_2Cl_2 and washed with 10 ml saturated $NaHCO_3$ aqueous solution. The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and filtered and the solvent was removed by vacuum. The residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 85:15) to afford 0.65 mmol (65%) of compound (1) which was characterized by TLC and mass spectra, M^+=196.3.

(2) Synthesis of DTrp-DPro-3-methylpiperidinamide (methylpiperidine) (2):

In a 100 ml round-bottom flask, 0.63 mmol of Boc-DTrp was dissolved in 25 ml dry CH_2Cl_2 0.66 mmol of 1-hydroxybenzotrizole was added while stirring under N2 atmosphere in an ice-bath. 0.63 mmol of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide HCL was added in 10 ml dry CH_2Cl_2 at a fast drop rate and the reaction mixture was washed with 20 ml of 20% citric acid aqueous solution, 20 ml of saturated $NaHCO_3$ aqueous solution and 20 ml of saturated sodium chloride aqueous solution. The organic layer was separated and dried over anhydrous magnesium sulfate,

filtered and concentrated in vacuum. Further purification was done by flash column chromatography ($CHCl_3$/MeOH, 95:5) to afford white solid of Boc-DTrp-DPro-3-piperidinamide.

Under N_2 atmosphere, the Boc-DTrp-DPro-3-piperidinamide was dissolved in 25 ml of CH_2Cl_2 and 10 ml of trifluoracetic was added while being stirred. The reaction mixture was stirred for 30 min. All volatiles were removed under vacuum and the residue was dissolved in 30 ml of CH_2Cl_2 and washed with 10 ml saturated $NaHCO_3$ aqueous solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuum. The residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 85:15) to afford 0.43 mmol (68.3%) of compound (2) which was characterized by TLC and mass spectra, M^+=382.46.

(3) Synthesis of Aib-DTrp-DPro-3-methylpiperidinamide (methylpiperidine) (YL-111):

In a 50 ml round bottom flask, 0.33 mmol of Boc-Aib was dissolved in 20 ml dry CH_2Cl_2 and then 0.31 mmol of 1-hydroxybenzotriazole was added while stirring under N_2 atmosphere in an ice-bath. 0.35 mmol of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide HCL was added in 10 ml dry CH_2Cl_2 at a fast drop rate and the reaction mixture was stirred for 1 hour at 0° C. 0.30 mmol of (2) in 15 ml of CH_2Cl_2 was added dropwise and stirring was continued for an additional 18 h at ambient temperature. The reaction mixture was washed with 20 ml of 20% citric acid aqueous solution, 20 ml of saturated $NaHCO_3$ aqueous solution and 20 ml of saturated sodium chloride aqueous solution. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum. Further purification was done by flash column chromatography ($CHCl_3$/MeOH, 95:5) to afford white solid of Boc-Aib-DTrp-DPro-3-piperidinamide.

Under N_2 atmosphere, the Boc-Aib-DTrp-DPro-3-piperidinamide was dissolved in 25 ml of CH_2Cl_2 and 10 ml of trifluoracetic acid was added while being stirred. The reaction mixture was stirred for 30 min. All volatiles were removed under vacuum and the residue was dissolved in 30 ml of CH_2Cl_2

and washed with 10 ml saturated $NaCHO_3$ aqueous solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuum. The residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 85:15) to afford 0.28 mmol (84.8%) of compound (YL-111) which was characterized by TLC and mass spectra M^+=468.6.

Biological Activity

In vitro and *in vivo* activity of certain compounds were determined in rats and adult beagle dogs (*in vivo* activity only). The results are described in Tables 3, 4, 5, 6 and 7 below.

The GHRP-2 (reference standard) has the structure DAla-DβNal-Ala-Trp-DPhe-Lys-NH_2 (Chen and Clarke, *J. Neuroend.* 7: 179 (1995)).

Table 3: *In Vitro* Release of Growth Hormone in Rat

Compound R^1-N_2-Aib DTrpX* Where X is:	**control**	**GHRP-2 .001**	**.0001**	**.0003**	**.001**	**.003**	**.01**	**.03**	**.1**	**.3**	**GH ng/ml 1**
DPro NH_2	752	1525	922	1102	997	1250	1535	1550	1716		
DPro-diiso-butylamide	523	1307					1322	1529	1427	1155	1124
R^1=N-2-Ohethyl DPro-diiso-butylamide	341	1427	- - -	- - -	452	326	526	820	1163	1217	
R^1=N_2N-di-2-OHethyl/ DPro diiso-butylamide	341	1427	- - -	- - -	433	395	446	592	905	1206	
R^1=N-ethyl/DPro diisobutyl-amide	510	1413	- - -	- - -	523	461	779	742	1079	1292	
R^1=Nentyl/ DPro diisobutyl-amide	341	1427	- - -	- - -	570	698	982	1307	1467	1387	
DPro-dipropyl-amide	543	1065	554	578	554	630	823	908	925		
DPro-butylamide	523	1307	512	647	833	995	1253	1612			
DPro-pentylamide	622	1290				569	830	1172	1184	1335	1451
DPro-dipentyl-amide	523	1307			1348	1561	1287	1021	1451		

Compound R^1-N_2-Aib DTrpX* Where X is:	control	GHRP-2 .001	.0001	.0003	.001	.003	.01	.03	.1	.3	GH ng/ ml 1
DPro-piperidine-3-methylbenzyl ether	389	821	529	553	721	728	886	978			
N,N-diethylnipecotamide	397	593	418	395	489	536	642				
-N-piperazine methyl-sulfonamide	553	1167		672	675	856	1049				
DPro-diethylamide	389	821	375	368	481	587	802	912			
DPro-m-methylpiper-idine	308	1052	434	458	633	837	968				
DPro-3,3-diphenyl-propylamide	466	1126			926	1118	1169	1177	1283		
DPro-4-piperidino-piperidin-amide	376	1125		419	451	540	808				
DPro-4-phenylpiper-idinamide	455	1520	624	777	1034	1186	1533	1772			
DPro-N-methyl-piperiazine	389	821	467	532	573	605	816	909			
DPro-2-morpholino-ethylamine	397	593	394	413	433	485	548				
DPro-spiroindole methyl-sulfonamide	385	915	440	512	691	819	956	922	1057		
DPro-pyrrolidine amide	614	1288	714	873	1149	1241					
DPro-indoline amide	486	1344			836	1127	1283	1235	1258	1220	1327
DPro-3-piperidine methanol amide	486	1344			1008	1199	1209	1348	1626	1567	
DPro-tropin amide	510	1220			542	797	1001	1124	1234		
DTrpPhe-Arg-5-amino pentamide	752	1525	1228	1416	1712	1648	1621				

* Unless otherwise stated, R^1 is H

Table 4: *In Vivo* Release of Growth Hormone in Rat

Compound R^1-N_2-AibDTrpX* Where X is:	**control**	**GHRP-2 .1**	**.1**	**.3**	**1**	**3**	**10**	**30**	**GH ng/ml 100**
DPro NH_2	223	1580	326	433	1159	2217	3155		
DPro-diisobutylamide	111	1066			642	1524	1837	2307	2913
R^1=N-2-OHethyl/ DPro-diiso-butylamide	92	2051	- - -	- - -	- - -	156	259	451	- - -
R^1=N,N-di-2-OHethyl/ DPro-diiso-butylamide	96	799	- - -	- - -	- - -		124	208	543
R^1=N -ethyl/ DPro-diiso-butylamide	92	2051	- - -	- - -	189	177	268	374	- - -
R^1=N -pentyl/ DPro-diiso-butylamide	92	2051	- - -	- - -	124	398	371	789	- - -
DPro-dipropylamide	91	1082	92	220	305	579	1646	2089	
DPro-butylamide	111	1066			196	329	647	2005	1596
DPro-pentylamide	170	1289			310	581	820	1660	2280
DPro-dipentylamide	128	1071	87	182	322	355	632	482	1206
DPro-piperidine-3-methyl-benzyl ether	150	1235			669	1725	2319		
N,N-diethylnipecot-amide	117	579		221	928	2070	2896	2186	
-N-piperazine methyl-sulfonamide	113	942		241	933	1965	1997		
DPro-diethylamide	128	919			448	766	1719	2465	3088
DPro-m-methylpiperidine	93	445				832	1557	1570	1762
DPro-3,3-diphenyl-propylamide	114	1106	141	147	138	249	383	624	
DPro-4-piperidino-piperidin-amide	150	1235				378	1318	2403	
DPro-4-phenylpiperidin-amide	111	568		112		238		499	
DPro-N-methyl-piperazine	128	919	218	425	1974	2314			
DPro-2-morpholino-ethylamine	111	568				900	1585	2195	
DPro-spiroindole methyl-sulfonamide	120	586				192	485	861	1177
DPro-pyrrolidine amide	98	1227				1024	2116	2381	
DPro-indoline amide	69	1279			142	317	269	885	
DPro-3-piperidine methanol amide	91	1082	155	668	1483	2616	2711		
DPro-tropin amide	73	1814		114	87	183	362	383	769
DTrpPhe-Arg-5-amino pentamide	109	1718	2628	2740	2272	2929			

* Unless otherwise stated, R^1 is H

Table 5: *In Vivo* Release of Growth Hormone in Adult Beagle Dogs

Compound R^1-N_2-AibDTrpX* Where X is:	**oral dose (mg/kg)**	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Time (hr) 8**
DPro NH_2	4	0.7	38	14	9.5	13	7.1	3.3	4	2.5	1.3
	4	0.8	54	30	15	12	4.8	4.2	3.4	1	0.8
DPro-diisobutylamide	4	0.8	27	9.4	14	22	22	21	11	6.9	5.4
	4	1.4	141	50	74	15	7.5	4	4.4	5.7	2.3
	2	0.6	54	30	22	15	7	4.6	4.8	2.7	1.8
	1	2.6	85	30	16	7.7	6	0.9	2.5	2.5	1.6
	1	<0.5	128	50	24	24	5.6	6.1	2.9	2.2	- -
	1	1.5	89	59	30	11	7	6.2	5.2	3.7	3.2
R^1=N-2-OHethyl/ DPro-diisobutyl-amide	1	3.8	102	26	25	10	6.1	5.6	4.0	5.2	5.0
	1	1	62	30	19	5.6	3.8	2.0	2.5	2.0	1.6
	1										
R^1=N_2N-di-2-OHethyl/ DPro-diisobutylamide	1										
R^1=N -ethyl/ DPro-diisobutyl-amide	4	1.3	100	29	20	9.4	3.9	2.2	2.4	1.5	5.6
	1	1.1	17	4.4	1.2	1.5	1.4	1.1	1.2	1.4	1.2
R^1=N -pentyl/ DPro-diisobutyl-amide	1										
DPro-dipropylamide	4	3.2	112	52	29	25	13	6.1	3.6	2.9	2.5
	1	0.6	27	19	5.6	1.6	1.6	0.6	1.4	0.8	0.8
DPro-butylamide	4	1.1	92	43	26	53	14	5.4	3.5	3.9	1.3
	2	1.8	60	40	13	3.8	3.7	2.2	2.6	2.4	1.7
DPro-pentylamide	4	1	72	12	11	6	4.9	3.5	2.5	1.9	1.4
DPro-dipentylamide	4	2.3	53	20	1.3	15	15	8.9	9.2	6.6	4.3
	4	3.7	32	11	8.4	7.2	3.6	3.5	2.3	2.7	<0.1
	4	2.9	11	11	15	3	3.3	2.5	2.7	2.3	2
DPro-piperidine-3-methyl-benzyl ether	4	2	>12	59	63	28	11	6.7	4.2	4.1	1.8
	4	0.8	8	28	27	11	14	14	11	4.7	6.8
	2	3.2	127	42	63	45	13	5.5	4.5	3.4	3.2
	2	3.6	169	39	23	6.3	4.5	1.7	2.7	2.3	1.9
	F0.5iv	2.9	112 81	78	27	9.3	4.5	4.1	2.9	4.1	4.1
N,N-diethylnipe-cotamide	4	1.7	57	13.	5.3	5.5	3.4	3.1	1.9	2	1.7
	4	0.9	43	8	2	2.1	0.8	0.9	2.1	6.9	0.9
	4F	2.7	6.3	7.3 3.5	3.7	2.2	0.9	10. 1	3.6	3.5	3.5
-N-piperazine methyl-sulfonamide	4	2.1	57	12. 5	8.7	3.8	1.7	2.2	1.6	6.3	3.2
DPro-diethylamide	4	2.4	56	38	29	28	16	9.1	6.2	3.9	2.8
	4	1.7	134	89	105	86	16	7.1	5.1	4.5	3.2
	F0.5iv	1.6	60	18	6	3.7	2.5	2	1.9	1.7	2.5
DPro-m-methylpiperidine	4	1	54	- -	50	52	20	27	8.1	9.6	1.7
	4F	1.4	72	84	18	4.7	3.5	1.4	1.1	1.6	1.5
	4	2.1	118	55	54	53	34	13	11	11	6.4
	2	1.2	128	59	29	12	8.9	3.6	3	3	1.7
	1	1.6	53	19	15	9.6	3.1	2.2	1.5	2.2	1
	1	2	63	32	17	13	12	1.5	2.4	3	2.2
DPro-3,3-diphenyl-propylamide	4	1.6	119	54	17	16	10	5.6	4.2	3.3	2.7
	4	2.2	54	12	8.6	7.4	13	5.9	3.4	3	ns
DPro-N-methyl-l-piperazine	4	1	100	22	8.3	7.9	4.8	2.6	2.9	2.3	1.8
	0.5iv	0.8	41	31	7	3.3	2.6	1.5	2.4	0.9	1.1
DPro-spiroindole methyl-sulfonamide	4	1.5	<0. 5	5.5	1.6	1.5	2.2	4.7	1.7	1.6	0.9
DPro-pyrrolidine amide	4	2.3	104	28	18	7.1	5.1	3.2	2.7	2.2	2.3
	4	2.1	63	32	45	30	11	6	4.9	4.1	3.6

Compound R^1-N_2-AibDTrpX* Where X is:	oral dose (mg/kg)	Time (hr) 0	0.5	1	2	3	4	5	6	7	8
DPro-indole amide	4	1.2	7	7.5	5.8	4.7	3.1	2.8	2.5	2	1.6
DPro-3-piperidine methanol amide	4	2.3	55	14	7.5	2.9	3.8	3.4	2.4	2.3	1.8
DPro-tropinamide	4	1.9	72	47	5.5	3.8	3.8	2.8	2.5	2.2	2.2
DTrpPhe-Arg-5-amino pentamide	2	3.1	83	20	6.8	3.9	2.9	3.3	3.1	3.3	3
	1	2.5	38	8.5	2.8	2.3	1.4	1.7	2.1	2	0.8

* Unless otherwise stated, R^1 is H

Table 6: *In Vivo* * Release of GH Rat

#	Compound iv	control	GHRP-2	GH ng/ml							
			.1	.01	.03	.1	.3	1	3	10	30
861	inipDαNalDTrpNH$_2$	145	1251					485	2197	2380	
1473	inipDαNalDValNH$_2$	145	1251					225		225	
1466	αAibDTrpDValNH$_2$	145	1251					124		418	
1415	αAibDTrpDProDSerNH$_2$	120	1465				820	1658	2306	2896	
1417	αAibDTrpDProDArgNH$_2$	120	1465				1362		2161	2057	
1246	αAibDTrpDProDPheNH$_2$	92	566			203	594	1901	2339		
1248	αAibDTrpDProDTrpNH$_2$	145	1343				229		1814		
1460	αAibDTrpDValDValNH$_2$	145	1343					104		240	
1461	αAibDValDProDValNH$_2$	145	1343					160		261	
1464	αAibDValDValDValNH$_2$	145	1343					96		197	
1468	αAibDTrpDProDLysNH$_2$	145	1343				157		791		
1462	αAibDProDProDValNH$_2$	145	1251					218		185	
1472	inipDαNalDTrpDValNH$_2$	145	1251			174	142	154	1019		
1489	αAibDTrpDProIleNH$_2$	135	1734			445	355	1884			
1476	αγAbuDαNalDTrpDIleNH$_2$	166	1175			97	111	152	152		
1495	inipDαNalDTrpDProIleNH$_2$	166	1175					824		1971	
1496	inipDαNalDTrpPheIleNH$_2$	166	1175					1638		2055	
1471	inipDαNalDTrpDValArgNH$_2$	145	1251			98	184	843			

#	Compound iv	control	GHRP-2	GH ng/ml							
			.1	.01	.03	.1	.3	1	3	10	30
1469	αAibDTrpDProDValDValNH$_2$	164	411				783	2450	1975		
1480	αAibDTrpDProDProDPalNH$_2$	78	990			245	622	2775			
1481	αAibDTrpDProDValArgDProNH$_2$	164	411			1703	2145	2278	2511		
1484	αAibDTrpDProDIleDArgNH$_2$	105	750	317	562	1863	2224	2446			
1475	αγAbuDTrpDTrpDIleNH$_2$	101	369			123	125	113			
1486	inipDαNalDTrpPheDValNH$_2$	101	369			203	352	1009			
1488	αAibDTrpDProValNH$_2$	105	750			323	644	1725			
1465	αAibDTrpDIleDIleNH$_2$	105	750					160			
1500	αAibDTrpDProLeuNH$_2$	225	1429				1831	2623			
1492	αAibDTrpDProThrNH$_2$	164	411			125	176	1031			
1497	DHisDTrpDProDValArgNH$_2$	164	411				154	181	235	601	
1451	DHisDTrpDProDThrNH$_2$	128	811(.03)				1380	2450	3133	2731	
		135	1734			898					
1452	αAibDTrpDProDIleNH$_2$	105	750			1028	1837	2138			
1474	αAibDTrpDPheDValNH$_2$	101	369			146	117	184			
1478	αAibDTrpDProDValDArgNH$_2$	124	1251			1420	2304	2245			
		135	1734			1177					
1293	αAibDTrpDProDAlaNH$_2$	157	1171			416	341	1682	3295		
1226	αAibDTrpDProDProNH$_2$	124	1072					2129			
1136	αAibDTrpDProArgNH$_2$	120	1465			297	670	1769	2644		

#	Compound iv	control	GHRP-2	GH ng/ml							
			.1	.01	.03	.1	.3	1	3	10	30
1251	αAibDTrpDProDValNH$_2$	188	439		228	832	1581	2405			
		120	1465			1584	2360	2181	3250		
1325	inipDαNalDTrpDProNH$_2$	120	1465					409	1203	2475	
1518	αAibDαNalDProDValDArgNH$_2$	99	1179		298	722	1695	2279			
1520	αAibDαNalDProDIleDArgNH$_2$	99	1179		325	640	1481	2497			
1487	αAibDTrpDProDProDLysNH$_2$	135	1734			171	676	1562			
1506	αAibHisDβNalDPheLysNH$_2$	136	1169			137	244	1416			
1507	αAibHisDTrpDProDValNH$_2$	136	1169			129	94	118			
1508	αAibHisDTrpDProDIleNH$_2$	136	1169			132	137	123			
1509	αAibHisDTrpDProValArgNH$_2$	136	1169			157	138	123			
1510	αAibHisDTrpDProDValArgNH$_2$	136	1169			145	133	246			
1511	αAibDβNalDProDValNH$_2$	136	1169			171	246	486			
1512	αAibDαNalDProDValNH$_2$	136	1169			143	141	611			
1523	αAibDTrpDProDThrArgNH$_2$	99	1179		1336	2219	2167	2781			
1524	αAibDTrpDProDNleArgNH$_2$	99	1179		1425	1952	2334	2164			
		17	1395	298	1151	2593	2275	2672			
1525	αAibDTrpDProDNValArgNH$_2$	99	1179		1397	2061	2285	2250			
		117	1395	146	580	1380	2047	1853			
1490	αAibDTrpDProIleArgNH$_2$	135	1734			173	202	179			
		105	750			137		397			

#	Compound iv	control	GHRP-2	GH ng/ml							
			.1	.01	.03	.1	.3	1	3	10	30
1479	αAibDTrpDProDProArgNH$_2$	101	369			2081	2566	2269			
1493	αAibDTrpDProProArgNH$_2$	225	1429				96	152	431		
1483	αAibDTrpDProDProDArgNH$_2$	135	1734			333		1838			
1485	αAibDTrpDProDIleArgNH$_2$	78	990	969	1472	1981	2073	3289			
1407	αAibDTrpDProPheDSerNH$_2$	138	1004						389	1365	
1137	αAibDTrpDProPheArgNH$_2$	120	1465			225	175	149			
1470	αAibDTrpDProDValArgNH$_2$	145	1251	600	1576	2647	2002	3414			
803	SarDTrpDTrpPheArgNH$_2$	120	1465				778	1894	2498		
1532	αAibDαNalDProDProArgNH$_2$	124	1012					1989			
1533	αAibDαNalDProDNValArgNH$_2$	124	1012					1910			
1519	αAibDαNalDProDIleArgNH$_2$	99	179		1641	1491	2354	2370			
1521	αAibDαNalDProDValLysNH$_2$	99	179		573	1372	2008	2355			
1530	αAibDαNalDProDThrArgNH$_2$	124	1012	388	317	1035	2873	2611			
1531	αAibDβNalDProDThrArgNH$_2$	124	1012					2303			
1513	αAibDβNalDProDValArgNH$_2$	136	1169			611	3230	3322			
1514	αAibDαNalDProDValArgNH$_2$	136	1169			1508	2710	2562			
		117	1395	404	687	1624	2516	2507			
1534	αAibDTrpDProDNleNH$_2$	120	1132			436	718	1968			
1535	αAibDTrpDProDNValNH$_2$	120	1132			228	614	1710			

#	Compound iv	control	GHRP-2	GH ng/ml							
			.1	.01	.03	.1	.3	1	3	10	30
	αAibDTrpDProDIle-X										
TJ 39	2-aminoethylamide	124	1012			1416	1739	2742	2931		
TJ 49	5-aminopentylamide	120	1132			1262	2822	2501	2426		
TJ 53	3-aminopropylamide	120	1132			575	1697	2603	1901		
	αAibDTrpDProDVal-X										
TJ 45	2-aminoethylamide	117	1395			813	1958	1736			
TJ 3	dimethylamide	135	1734			247	836	1362	1805		
TJ 8	diethylamide	135	1734			232	255	366	1157		
	αAibDTrpDProDPro-X										
TJ 28	2-aminoethylamide	73	766			151	339	558	920	1999	
353	DβNalAlaTrpDPheLysGlnGlyNH$_2$	90	1542			879	1307	1268	2729		
359	DAlaDTrpAlaTrpDPheLysValGlyNH$_2$	151				2553	3653	2530			
		90	1542		452	1763	3364	3003			
371	DAlaDβNalAlaTrpDPheLysGlnGlyGlyGlyNH$_2$	157	983	535	1834	2176	2116	3995			
356	DAlaDTrpAlaTrpDPheLysHisGlyNH$_2$	90	1542			1252	2811	1886			

Table 7: *In Vivo** Release of GH in Adult Beagle Dogs

#	Compound	oral dose mg/kg	Time (hr)									
			0	0.5	1	2	3	4	5	6	7	8
			Canine GH ng/ml									
	αAibDTrpDProDIleX											
TJ49	5-aminopentylamide	1	5.4	123	27	21	20	5.6	2.3	1.2	0.8	1.4
		1	3.8	116	20	5.7	13	19	3.3	1.1	1	1.1
TJ53	3-aminopropylamide	1	6	44	19	22	7.8	6.4	6.7	5.4	6.4	6.9
		1	5.9	91	32	19	7.3	6.2	13.2	6.6	4.7	5.6
TJ39	2-aminoethylamide	1	5.7	31	11	10	10	4	4.4	3.8	5.1	3.4
		1	3.4	99	21	19	14	9.1	4.6	4	4.2	3.8
TJ66	4-aminobutylamide	1	1.8	100	20	19	4	2.8	2.7	2.1	3.4	2.8
	αAibDTrpDProDValX											
TJ6	N-dimethylamide	1	5.1	9.5	5.4	5.6	5.5	6	6.2	5	6.4	3.8
TJ8	N-diethylamide	1	20	8.7	5	15	6	4.4	4.8	5.1	4.3	4.4
TJ45	2-aminoethylamide	1	6.4	97	26	24	8	3	6	12	9	8
		1	7.6	52	24	21	13	9	8	9	8	8
	αAibDTrpDProDValX											
TJ61	5-aminopentylamide	1	3.7	41	12	5.3	4.4	4.1	3.7	3.5	4.8	4.1
		1	2.3	91	17	26	7.6	4.2	3.5	3	3.8	2.7

#	Compound	oral dose mg/kg	Time (hr)									
			0	0.5	1	2	3	4	5	6	7	8
			Canine GH ng/ml									
	αAibDTrpDProDNleX											
TJ59	5-aminopentylamide	1	6.4	54	16	13	5	5	5.1	6.9	6.4	5.9
		1	6.7	112	19	14	13	7.4	6.6	7.1	6.4	5.4
1476	αAibDTrpDProDValDArgNH$_2$	2	3.2	42	31	13	25	5	3.1	4.1	2.6	1.7
1513	αAibDβNalDProDValArgNH$_2$	1	6.6	128	38	47	35	25	8.7	6.5	6.9	7.2
		1	5.3	125	22	8.7	6.3	5	3.6	3.6	6.7	3.6
1514	αAibDαNalDProDValArgNH$_2$	1	3.5	31	10	5.8	5.4	4.2	3.2	3.8	3.4	3.6
		1	3.5	126	24	31	14	7.3	3.5	4.8	3.1	4.9
1519	αAibDαNalDProDIleArgNH$_2$	1	6.8	72	28	21	13	6.5	5.5	4.4	6.9	5.2
1521	αAibDαNalDProDValLysNH$_2$	1	3.7	111	39	61	29	14	8.2	4	4.4	4.7
973	inipDαNalDβNalPheArgNH$_2$	2	3.1	13	4.2	3.3	2.5	2.1	2.9	2.3	2.9	2.4
1536	αAibDTrpDProDIleArgGlyNH$_2$	0.5	1.5	93	23	29	8.2	6.5	5.5	4.3	4.3	2.9
1537	αAibDTprDProDNleArgGlyNH$_2$	0.5	3.7	76	12	10	2.6	3.1	2.3	2.3	2.8	2.8
1539	αAibDTrpDProDThrArgGlyNH$_2$	0.5	1.8	86	28	85	13	7.6	4.8	2.7	2.7	2.3
1252	αAibDTrpDProDGlnNH$_2$	2	1.5	2.6	6.4	3.5	2.8	2.5	2.3	1.9	1.9	2
869	InipDαNalDTrpPheCOOH	2	2.6	3.5	2	2.6	2.7	2.6	2.5	3.6	3.6	3.2
		1	1.4	1.8	1.3	1.5	1.3	2.1	1.9	2.6	1.4	2.1
956	InipDαNalDTrpValNH$_2$	1	4.2	3.3	3.9	4	3.6	5.5	3.4	3.8	2.3	3.1

#	Compound	oral dose mg/kg	Time (hr) 0	0.5	1	2	3	4	5	6	7	8
			Canine GH ng/ml									
1136	αAibDTrpDProArgNH$_2$	1.1	4.9	15	8.3	6.3	4.8	5.2	4.8	4.3	5.1	4.8
		1	1.7	27	8.7	1.5	1.9	1.9	2.4	2.7	1.6	2.7
1118	αAibDTrpDProCHαAlaNH$_2$	1	6.6	3.8	2.6	2.6	2.8	2.8	1.9	2.1	2.9	2.6
1251	αAibDTrpDProDValNH$_2$	2	2.9	47	16	14	7.8	5.6	4.7	5.6	6.8	4.9
		2	1.6	28	5.6	4.1	4.1	4	4.1	4.2	3	2.6
		1.1	2.4	128	31	42	5.5	4.8	4.4	3.4	4.4	3.4
1293	αAibDTrpDProDAlaNH$_2$	2	4.6	11	4.9	4.9	4.6	5.5	5.9	4	4.7	4.7
		2	2.9	15	8.9	11	4	3.8	3	2.7	3.6	2.7
		2	3.9	14	6.2	3.8	2.7	1.9	2.9	2.4	3.4	3.1
1452	αAibDTrpDProDIleNH$_2$	2	2.5	117	23	13	4.1	3.6	5	4.3	5.2	4.7
1451	αAibDTrpDProDThrNH$_2$	2	1.4	20	4	3.9	2.7	2	1.7	2.5	2.6	1.6
		1.6	3.3	51	22	58	7.1	5.6	4.9	4.6	4.6	4.1
1246	αAibDTrpDProDPheNH$_2$	2	1.7	29	20	9.2	3.7	2.7	1.6	1.9	2.4	1.8
1474	αAibDTrpDPheDValNH$_2$	2	3.2	2.9	2.8	2.7	2.9	2.9	2.8	2.8	4.7	2.7
1248	αAibDTrpDProDTrpNH$_2$	2	1.8	5.9	2.7	1.4	2.2	1.8	1.7	1.3	3.2	3.3
1479	αAibDTrpDProDProArgNH$_2$	1.8	2	38	9.3	6.2	6.1	6	5.7	4.7	2.7	2.1
1478	αAibDTrpDProDValDArgNH$_2$	2	3.2	42	31	13	25	5	3.1	4.1	2.6	1.7
1470	αAibDTrpDProDValArgNH$_2$	2	3.6	62	26	30	30	6.8	13	14	6.5	5.4
		2	3.4	37	32	41	13	23	9.2	8	4.9	4.1

#	Compound	oral dose mg/kg	Time (hr) 0	0.5	1	2	3	4	5	6	7	8
			Canine GH ng/ml									
		1	5.1	32	14	18	16	14	11	6.3	6.3	5.2
1485	αAibDTrpDProDIleArgNH$_2$	2	4.9	102	19	48	23	11	8	9	16	21
		2	5.7	49	38	26	10	21	7.6	6.7	10	11
		2	3.5	20	17	15	16	18	13	19	13	14
		2	1.2	60	34	15	9.2		5.3		4.5	4.7
		1	4.6	136	23	95	14	22	8.3	6.9	4.9	5.2
		1	6.7	104	47	84	41	29	15	19	15	5.4
		1	5.2	50	17	11	6.9	6.8	6.2	7.1	6.7	4.5
		0.5	6	110	63	32	13	12	4.9	5	5.6	5.4
		0.5	7.8	109	78	54	49	97	52	51	22	16
		0.5	6.1	126	78	32	12	7.8	4.3	15	9.2	3.6
		0.5	6.6	125	57	35	20	11	40	15	8	8
		0.5	5.9	227	28	26	40	13	50	9	7	7
		0.25	3.5	102	35	32	28	5.8	3.7	4.1	5	6.9
		0.25	2.1	53	13	10		3.1	2.1	4	3.3	4.4
		0.125	3.6	48	23	7.9	3.8	3	3.9	3	5.7	3.4
		0.125	2.6	53	16	7.6	3.3	3.9	3.9	3.6	5.3	3.2
1523	αAibDTrpDProDThrArgNH$_2$	1	5.4	105	63	40	30	15	8	9.3	7.9	4
1524	αAibDTrpDProDNleArgNH$_2$	1	5.3	110	105	128	38	25	18	7.8	4.5	3.8

#	Compound	oral dose mg/kg	Time (hr)									
			0	0.5	1	2	3	4	5	6	7	8
			Canine GH ng/ml									
		0.5	5.6	72	23	10	7.1	7.1	6.7	6.4	5.9	5.6
1525	αAibDTrpDProDNValArgNH$_2$	0.5	6	99	58	26	13	7.8	6.2	6	5.7	4.6
TJ64	5-aminopentylamide	1	1.5	32	13	5.6	3.5	2.3	2.7	1.4	2.9	3.2

IN THE CLAIMS:

1. A compound having the formula

$A_{1'}$-Y,

wherein $A_{1'}$ is Aib, inip, ABU, βAla, His, Sar or any of their respective D-isomers;

Y is $A_{2'}$-A_3-A_4-A_5-A_6-Z';

$A_{2'}$-A_3-A_4-A_5-Z' or $A_{2'}$-A_3-A_4-Z';

wherein $A_{2'}$ is A_5-$A_{2''}$ or $A_{2''}$;

wherein A_5 is a spacer amino acid;

$A_{2''}$ is any natural L-amino acid, Pal, or their respective D-isomers, DαNal or DβNal;

A_3, A_4 and A_5 are any natural L-amino acid, Pal, αNal, βNal, Nle, Arg-DPro, DPCl, D or L cyclohexyl-amino acid, or any of their respective D-isomers; and

Z' is NH_2, OH, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl) amino, amino-C_1-C_{10} alkylamino or di(amino C_1-C_{10} alkyl) amino;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, having the formula Aib-Y.

3. The compound of claim 2, wherein Aib is αAib.

4. The compound of claim 2, wherein the Aib residue is substituted or unsubstituted.

5. The compound of claim 4, wherein Aib is substituted and the substituents are selected from the group consisting of N- and N-, N-C_1-C_6 alkyl, halogens, N- and N-, N-2 hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and 3-hydroxyisobutyl.

6. The compound of claim 2, wherein Aib is unsubstituted.

7. The compound of claim 1, wherein $A_{1'}$ is Aib, inip or ABU.

8. The compound of claim 7, wherein $A_{1'}$ is ABU and ABU is γABU or α,γABU.

9. The compound of claim 1, 2, 3, 4, 5 or 6, wherein $A_{2''}$ is DTrp, DαNal or DβNal.

10. The compound of claim 9, wherein $A_{2''}$ is DTrp.

11. The compound of claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 wherein A_3 is DPro or DTrp;

12. The compound of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, wherein A_4 is Gly, Phe, Pro, Ile, DPro, DPhe, DPal, DLeu, DHis, DVal, DGln, DIle, DNle, DArg, DAla, DSer, DThr, DIle, Arg, Orn Lys, Ala, Pal, Thr, Val, Phe, DTrp, DNVal, DNle or D or L cyclohexylalanine.

13. The compound of claim 12, wherein A_4 is DSer, DArg, DPro, DTrp, DVal, DIle, DThr, DNVal, DNle, Ile, Pro, Phe.

14. The compound of claim 13, wherein A_4 is DPro, DTrp, DIle or DNle.

15. The compound of claim 14, wherein A_4 is DPro.

16. The compound of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 wherein A_5 is Ile, Arg, Pal, DArg, DSer, Lys or Arg-DPro or DLys.

17. The compound of claim 16, wherein A_5 is Arg, DArg, Lys or DLys.

18. The compound of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17, wherein Z' is C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amino-C_1-C_{10} alkylamino or di(amino C_1-C_{10} alkyl) amino.

19. The compound of claim 18, wherein Z' is 2-aminoethylamide, -3-aminopropylamide, -4-aminobutylamide, -5-aminopentylamide, -6-aminohexylamide, mono or dimethylamide, mono or diethylamide, mono or dipropylamide.

20. The compound of claims 1, 2 or 3 wherein Y is $A_{2''}$-DPro-A_4-A_5-A_6-Z', $A_{2''}$-A_3-A_4-Z' or $A_{2''}$-A_3-A_4-A_5-Z'.

21. The compound of claim 20, wherein Y is $A_{2''}$-DPro-A_4-Z', or $A_{2''}$-DPro-A_4-A_5-Z'.

22. The compound of claim 21, wherein Y is $A_{2''}$-DPro-A_4-A_5-Z'.

23. The compound of claims 1, 2 or 3, wherein Z' is $-NH_2$.

24. The compound of claim 3, selected from the group consisting of αAib-DTrp-DPro-A_4-A_5-A_6-Z', αAib-DTrp-DPro-A_4-A_5-Z', αAib-DTrp-DPro-A_4-Z', αAib-DTrp-DPro-A_4-Arg-NH_2, αAib-DTrp-DPro-A_4-Arg-A_6-NH_2, αAib-DTrp-DPro-A_4-Arg-Gly-NH_2, αAib-DαNal-DPro-A_4-A_5-A_6-Z', αAib-DαNal-DPro-A_4-A_5-Z', αAib-DαNal-DPro-A_4-Z', αAib-DαNal-DPro-A_4-NH_2, αAib-DαNal-DPro-A_4-Arg-NH_2, and αAib-DαNal-DPro-A_4-Arg-Gly-NH_2.

25. The compound of claim 24, wherein A_4 is DIle, DThr, DNle, DVal, DGln, DAla, DPhe, DTrp, DNVal and Arg.

26. The compound of claim 1 which is selected from the group consisting of αAibDTrpDProDIleArgNH_2, αAibDTrpDProDThrArgNH_2, αAibDTrpDProDValArgNH_2, αAibDTrpDProDNleArgNH_2, and αAibDαNalDProDIleDArgNH_2.

27. The compound of claim 1, which is selected from the group consisting of αAib-$A_{2'}$-DPro-A_4-Z, αAib-DTrp-DPro-DThr-NH_2, αAib-DTrp-DPro-DGln-NH_2, αAib-DTrp-DPro-Arg-NH_2, αAib-DTrp-DPro-DAla-NH_2, αAib-DTrp-DPro-DPhe-NH_2, αAib-DTrp-DPro-DTrp-NH_2, αAib-DTrp-DPro-DVal-NH_2, αAib-DTrp-DPro-DNVal-NH_2, and αAib-DTrp-DPro-DIle-NH_2.

28. The compound of claim 1, which is selected from the group consisting of αAib-DTrp-DPro-DIle-Arg-Gly-NH_2, αAib-DTrp-DPro-DThr-Arg-Gly-NH_2, and αAib-DTrp-DPro-DNle-Arg-Gly-NH_2.

29. A compound selected from the group consisting of inipDαNalDTrpNH_2, inipDαNalDValNH_2, αAibDTrpDValNH_2, αAibDTrpDProDSerNH_2, αAibDTrpDProDArgNH_2, αAibDTrpDProDPheNH_2, αAibDTrpDProDTrpNH_2, αAibDTrpDValDValNH_2, αAibDValDProDValNH_2, αAibDValDValDValNH_2, αAibDTrpDProDLysNH_2, αAibDProDProDValNH_2, inipDαNalDTrpDValNH_2, αAibDTrpDProIleNH_2, αγAbuDαNalDTrpDIleNH_2, inipDαNalDTrpDProIleNH_2, inipDαNalDTrpPheIleNH_2, inipDαNalDTrpDValArgNH_2, αAibDTrpDProDValDValNH_2, αAibDTrpDProDProDPalNH_2, αAibDTrpDProDValArgDProNH_2, αAibDTrpDProDIleDArgNH_2, αγAbuDTrpDTrpDIleNH_2, inipDαNalDTrpPheDValNH_2, αAibDTrpDProValNH_2; αAibDTrpDIleDIleNH_2, αAibDTrpDProLeuNH_2, αAibDTrpDProThrNH_2, DHisDTrpDProDValArgNH_2, DHisDTrpDProDThrNH_2, αAibDTrpDProDIleNH_2, αAibDTrpDPheDValNH_2, αAibDTrpDProDValDArgNH_2, αAibDTrpDProDAlaNH_2, αAibDTrpDProDProNH_2, αAibDTrpDProArgNH_2, αAibDTrpDProDValNH_2, inipDαNalDTrpDProNH_2, αAibDαNalDProDValDArgNH_2, αAibDαNalDProDIleDArgNH_2, αAibDTrpDProDProDLysNH_2, αAibHisDαNalDPheLysNH_2, αAibHisDTrpDProDValNH_2, αAibHisDTrpDProDIleNH_2, αAibHisDTrpDProValArgNH_2,

αAibHisDTrpDProDValArgNH$_2$, αAibDαNalDProDValNH$_2$,
αAibDTrpDProDThrArgNH$_2$, αAibDTrpDProDNleArgNH$_2$,
αAibDTrpDProDNValArgNH$_2$, αAibDTrpDProIleArgNH$_2$,
αAibDTrpDProDProArgNH$_2$, αAibDTrpDProProArgNH$_2$,
αAibDTrpDProDProDArgNH$_2$, αAibDTrpDProDIleArgNH$_2$,
αAibDTrpDProPheDSerNH$_2$, αAibDTrpDProPheArgNH$_2$,
αAibDTrpDProDValArgNH$_2$, SarDTrpDTrpPheArgNH$_2$,
αAibDαNalDProDProArgNH$_2$, αAibDαNalDProDNValArgNH$_2$,
αAibDαNalDProDIleArgNH$_2$, αAibDαNalDProDValLysNH$_2$,
αAibDαNalDProDThrArgNH$_2$, αAibDαNalDProDThrArgNH$_2$,
αAibDαNalDProDValArgNH$_2$, αAibDαNalDProDValArgNH$_2$,
αAibDTrpDProDNleNH$_2$, αAibDTrpDProDNValNH$_2$,
αAibDTrpDProDProArgNH$_2$, αAibDTrpDProDValDArgNH$_2$,
αAibDTrpDProDValArgNH$_2$, αAibDTrpDProDIleArgNH$_2$,
αAibDαNalDProDValArgNH$_2$, αAibDαNalDProDValArgNH$_2$,
αAibDαNalDProDIleArgNH$_2$, αAibDαNalDProDValLysNH$_2$,
inipDαNalDαNalPheArgNH$_2$, αAibDTrpDProDThrArgNH$_2$,
αAibDTrDProDNleArgNH$_2$, αAibDTrpDProDNValArgNH$_2$,
αAibDTrpDProDIleArgGlyNH$_2$, αAibDTrpDProDProDIleArgGlyNH$_2$,
αAibDTprDProDNleArgGlyNH$_2$, αAibDTrpDProDThrArgGlyNH$_2$,
αAibDTrpDProDProA$_4$ArgNH$_2$, αAibDTrpDProDProA$_4$ArgGlyNH$_2$,
αAibDTrpDProDIleArgNH$_2$, αAibDTrpDProDIleArgGlyNH$_2$,
αAibDTrpDProDProDIleArgNH$_2$, αAibDTrpDProDProDIleArgGlyNH$_2$,
DβNalAlaTrpDPheLysGlnGlyNH$_2$, DAlaDTrpAlaTrpDPheLysValGlyNH$_2$,
DAlaDβNalAlaTrpDPheLysGlnGlyGlyGlyNH$_2$, and
DAlaDTrpAlaTrpDPheLysHisGlyNH$_2$.

30. A compound of the formula A_1-A_2-X, wherein A_1 is Aib, inip or ABU; A_2 is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal; and

X is (1) R_1-R_2-Z, wherein R_1 and R_2 are any natural L-amino acid, Pal, αNal, βNal, DpCl, CHx, where CH_x is cyclohexyl, CHxAla, or any of their respective D-isomers; and Z is $CONH_2$ or COOH;

(2) $DpR_3Phe\text{-}R_4\text{-}Z$, wherein R_3 is a halogen; R_4 is L-amino acid or Pal, or their respective D-isomers; and Z is $CONH_2$ or COOH;

(3) $NH(CH_2)_nNH$, where n is 1 to 8;

(4) $R_5\text{-}R_6$, wherein R_5 is any natural L-amino acid, Pal, αNal, βNal, DpCl, CHx, or any of their respective D-isomers; and R_6 is diisobutylamide, dipropylamide, butylamide, pentylamide, dipentylamide, or C(=0)(substituted heteroalicyclic or heteroaromatic);

(5) DTrp Phe $ArgR_7$, wherein R_7 is $NH(CH_2)_nNH$, where n is 1 to 8; or

(6) $R_8\text{-}R_9\text{-}R_{10}\text{-}Z$, wherein R_8 is DTrp, DPro, DαNal or DβNal; R_9 is any natural L-amino acid or Pal, or their respective D-isomers; R_{10} is any natural L-amino acid or Pal, or their respective D-isomers; and Z is $CONH_2$ or COOH.

31. A compound of the formula $A_{1'}\text{-}X'$, wherein $A_{1'}$ is Aib, inip, ABU, IMC, Ava, 4-IMA, βAla, Ileu, Trp, His, DpCl, CHx where CH_x is cyclohexyl, or any of their respective D-isomers; and

X' is (1) $R_{1'}\text{-}R_{2'}\text{-}Z'$, wherein R_1 is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal; and R2 is any natural L-amino acid, Pal, αNal, βNal, DpCl, Aib, CHx, or CHxAla, or any of their respective D-isomers; and Z is $CONH_2$ or COOH; or

(2) $R_3\text{-}R_4$, wherein R_3 is any natural L-amino acid or Pal, or their respective D-isomers, DαNal or DβNal; and R_4 is $NH(CH_2)_nNH$, where n is 1 to 8.

32. The compound of claim 30, wherein A_1 is αAib, and A_2 is selected from the group consisting of DTrp and DαNal.

33. The compound of claim 30, wherein A_1 is αAib; A_2 is DTrp; X is $R_1\text{-}R_2\text{-}Z$, where R_1 is DPro, R_2 is selected from the group consisting of Gly, Phe, Pro, DPro, DPhe, DPal, DLeu, DHis, DVal, DGln, DArg, DAla, DSer, DThr and DIleu, and Z is $CONH_2$.

34. The compound of claim 30, wherein A_1 is α,γABU and A_2 is selected from the group consisting of DTrp and DαNal.

35. The compound of claim 34, wherein X is R_1-R_2-Z, where R_1 is DTrp, R_2 is selected from the group consisting of Arg, Lys and Orn, and Z is $CONH_2$.

36. The compound of claim 30, wherein A_1 is inip, A_2 is DαNal and X is R_1-R_2-Z, where R_1 is DTrp, R_2 is selected from the group consisting of Phe, Pal, CHx Val, Thr, Arg, Lys and Pro, and Z is $CONH_2$.

37. The compound of claim 30, wherein A_2 is DTrp, DαNal or DβNal; and

X is (1) R_5-R_6, where R_5 is selected from the group consisting of DTrp and DPro; and R_6 is diisobutylamide, dipropylamide, butylamide, pentylamide, dipentylamide, or C(=0) (substituted heteroalicyclic or heteroaromatic); or

(2) DTrp Phe ArgR_7, wherein R_7 is $NH(CH_2)_nNH$, where n is 1 to 8.

38. The compound of claim 37, wherein R_6 is DPro-C(=0) (substituted heteroalicyclic or heteroaromatic), wherein the heteroatom is selected from the group consisting of O, N, S and P.

39. The compound of claim 38, wherein the heteroalicyclic moiety contains 2 to 12 carbon atoms and the heteroaromatic moiety contains 5 to 12 carbon atoms.

40. The compound of claim 39, wherein the C(=0) (substituted heteroalicyclic or heteroaromatic) moiety is selected from the group consisting of piperidine-3-methyl-benzylether, N-diethylnipectamide, N-piperazine methylsulfonamide, diethylamide, m-methylpiperidine, 3,3-diphenylpropylamide, 4-piperidino piperidinamide, 4-phenyl-piperidinamide, N-methyl 1-piperiazine, 2-morpholinoethylamine, spiroindole methylsulfonamide, pyrrolidine amide, indoleamide, 3-piperidine methanol amide, and tropin amide.

41. The compound of claim 37 wherein X is $DProNH_2$, DPro-diisobutylamide, DPro-butylamide, DPro-C(=0) (substituted heteroalicyclic or heteroaromatic), or DTrp-Phe-Arg-5-aminopentamide.

42. The compound of claim 30, wherein X is R_8-R_9-R_{10}-Z, wherein R_8 is selected from the group consisting of DTrp or DPro; R_9 is selected from the group consisting of Phe or DVal; R_{10} is selected from the group consisting of Lys or Arg; and Z is $CONH_2$

43. A method of promoting the release and elevation of blood growth hormone levels by administering the compound of claim 1, 2, 3, 30, 31 or 37 in a synergistic amount with a second compound, wherein the second compound is a compound which acts as an agonist at the growth hormone releasing hormone receptor or inhibits the release of somatostatin.

44. A pharmaceutical composition comprising the compound of claim 1, 30 or 37 and the pharmaceutically acceptable carrier or diluent.

45. The pharmaceutical composition of claim 44, which further comprises a second compound which acts as an agonist at the growth hormone releasing hormone receptor or inhibits the effects of somatostatin.

46. A method of promoting the release and elevation of blood hormone levels by administering the peptide of claim 1, 2. 3, 30 or 37 with at least a naturally occurring growth hormone releasing hormone and functional equivalents thereof, or a compound which promotes the release of growth hormone.

47. A method for treating hypothalamic pituitary dwarfism, osteoporosis or burns, which comprises administering a therapeutically effective amount of the peptide of claim 1, 30 or 31.

48. A method for promoting wound healing, promoting recovery from surgery or recovery from acute/chronic debilitating illnesses which comprises administering a therapeutically effective amount of the pharmaceutical composition of claim 44.

49. A method for prevention or reduction of cachexia in cancer patients which comprises providing a therapeutically effective amount of the compound of claim 1, 30 or 31.

50. A method for promoting anabolism and/or to prevent catabolism in humans which comprises administering a therapeutically effective amount of the compound of claim 1, 30 or 31.

51. The method of claim 50, wherein the therapeutically effective amount is about 30 μg to 1200 μg of the peptide per kg of body weight.

52. A method for increasing muscle in an animal and/or decreasing body fat which comprises administering an effective amount of the compound of claim 1, 30 or 31.

53. A method for improving serum lipid pattern in humans by decreasing in the serum the amount of serum cholesterol and low density lipoprotein and increasing in the serum the amount of the high density lipoprotein which comprises administering an effective amount of the compound of claim 1, 30 or 31.

54. The method of claim 52 wherein the effective amount ranges between about 0.1 μg to 10 μg of total peptide per kg of body weight.

55. The method of claim 53, wherein the effective amount ranges between about 0.1 μg to 10 μg to total peptide per kg of body weight.

56. A method for descreasing atherosclorosis which comprises administering an effective amount of the compound of claim 1, 30 or 31.

57. A method to improve cardiac performance in congestive heart failure and in patients with cardiac myopathy which comprises administering an effective amount of the compound of claim 1, 30 or 31.

58. A method to improve sleep which comprises administering an effective amount of the compound of claim 1, 30 or 31.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 February 2000 (24.02.2000)

PCT

(10) International Publication Number
WO 00/09537 A3

(51) International Patent Classification[7]: C07K 5/10, 7/06, 7/02, 5/02, A61K 38/07, 38/08, A61P 5/02, C07K 14/60

(21) International Application Number: PCT/US99/17867

(22) International Filing Date: 6 August 1999 (06.08.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/096,795	14 August 1998 (14.08.1998)	US
60/129,806	16 April 1999 (16.04.1999)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US Not furnished (CIP)
Filed on Not furnished

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
20 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/09537 A3

(54) Title: COMPOUNDS HAVING GROWTH HORMONE RELEASING ACTIVITY

(57) Abstract: Compounds that promote growth hormone releasing activity are disclosed. These compounds have the formula: A_1-A_2-X; A_1-X', or A_1-Y. These compounds can be present in a pharmaceutical composition. The compounds can be used with a second compound that acts as an agonist at the growth hormone releasing hormone receptor or which inhibits the effects of somatostatin. These compounds can be used for a variety of uses such as treating hypothalamic pituitary dwarfism, osteoporosis, burns, or promoting wound healing.

INTERNATIONAL SEARCH REPORT

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PCT/US 99/17867

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/10 C07K7/06 C07K7/02 C07K5/02 A61K38/07
A61K38/08 A61P5/02 C07K14/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2001	07/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 99/17867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DEGHENGHI R ET AL: "GH-RELEASING ACTIVITY OF HEXARELIN, A NEW GROWTH HORMONE RELEASING PEPTIDE, IN INFANT AND ADULT RATS" LIFE SCIENCES,GB,PERGAMON PRESS, OXFORD, vol. 54, no. 18, 1994, pages 1321-1328, XP000651534 ISSN: 0024-3205 ---	
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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/17867

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-23,30-32,34,42-58 (all partially)

Present claims 1-23,30-32,34,42-58 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, a peptide sequence consisting virtually only of variables cannot be considered to be a clear and concise definition of patentable subject-matter (art. 6 PCT). The claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for all peptides listed in claims 24-29 and extended to those parts of the claims which appear to be adequately supported and disclosed, namely for claims 33 and 35-41, defining the peptide N-terminal portion.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intr ional Application No
PCT/US 99/17867

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Int ional Application No
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